NIDDK

Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) Global Data Dictionary

NASH CRN Study Databases as of 30 July 2017

- NAFLD Database (Adults and Pediatric)
- PIVENS RCT (Adult)
- TONIC trial (Pediatric)
- NAFLD Adult and Pediatric Database 2
- FLINT RCT (Adult)
- CyNCh RCT (Pediatric)

Key to Global Dictionary Data Items:

By design, Case Report Form Item numbers and names and the SAS variable names and labels are in one-to-one correspondence.

All Case Report form item numbers are linked directly to SAS variable names and variable labels. If you have the case report form revision number and the form item name, you have the SAS database variable name, and vice versa.

For example, the Registration Form (*RG*), Revision 1, Item Number (12), "*Ethnic Category*" for the NAFLD Database study has the corresponding SAS variable name: *rg112* with SAS variable label: "*Ethnic Category*." Symbolically, if *ff* = 2-digit form abbreviation, *r* = 1-digit form revision number, and *iii* is the item number, the SAS variable name is *ffriii*.

More Examples:

- Baseline History case report form (BG), Revision 2, Item (20v), "Edema," for the FLINT trial, has corresponding SAS variable name bg220v and SAS variable label "Edema."
- Central Histology Review (CR) form, Revision 3, item (15a), "Liver cell injury: Ballooning" for the NAFLD Database 2 study has SAS variable name cr315a and SAS variable label "Ballooning."

Prepared by the NASH CRN DCC

Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
ΑE	Adverse Event Report
AN	Serious Adverse Event Report
ВС	Blood Collection for DNA
BD	Food Questionnaire Documentation
BG	Baseline History
ВН	Baseline History
BP	Blood Processing for Plasma and Serum
BQ	Beverage Questionnaire (BEVQ-15)
CF	Continuation Form
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
CV	Cardiovascular Risk Factors
DD	DEXA Scan for Bone Mineral Density
DR	Death Report
DX	DEXA Scan for Body Fat
EC	Eligibility Checklist
ED	Database Enrollment
EN	Database 2 Enrollment
FI	Family Member Identification
FH	Follow-up Medical History
FR	FibroScan® Report
HC	Hepatocellular Carcinoma Report
HE	Histology Findings for Most Recent Liver Biopsy Done Prior to Database Registration
HF	Liver Biopsy Histology Findings
HG	Histology Findings for Next Most Recent Liver Biopsy Done Prior to Database Registration
HI	Follow-up Medical History
HS	Steatohepatitis Determination – 1 st Reading
HT	Steatohepatitis Determination –2 nd Reading
IE	Interim Event Report

IR	Liver Imaging Studies Report
LD	Lifetime Drinking History (Skinner)
LP	Symptoms of Liver Disease (Children)
LQ	Symptoms of Liver Disease
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LT	Liver Tissue Banking
LU	Laboratory Results - Tests Required at Visit s2
MA	Modifiable Activity Questionnaire
MR	MRI Report
MV	Missed or Incomplete Visit
ND	Nutrition Data Documentation
PA	Physical Activity
PE	Physical Examination
PF	Focused Physical Examination
PQ	Pediatric QOL: Parent Report for Teens (Age 13-17)
PR	Pediatric QOL: Parent Report for Children (Age 8-12)
PS	Pediatric QOL: Parent Report for Young Children (Age 5-7)
PT	Pediatric QOL: Parent Report for Toddlers (Age 2-4)
PV	Pediatric QOL: Young Child Report (Age 5-7)
PW	Pediatric QOL: Child Report (Age 8-12)
PY	Pediatric QOL: Teen Report (Age 13-17)
QF	MOS 36-Item Short-Form Health Survey
RC	Rescreen Form
RD	Study Drug Dispensing and Return
RG	Registration
RZ	Randomization Checks
SD	Liver Biopsy Materials Documentation
SE	Most Recent Prior Liver Biopsy Materials Documentation
SF	Next Most Recent Prior Liver Biopsy Materials Documentation
SR	Serious Adverse Event/IND Safety Report
TN	Transfer Notification

NASH CRN Study Outcomes

Case-Report Forms
(For collection of outcome data)

CONFIDENTIAL: Not for Citation or Distribution

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee.

By whom: Data Coordinating Center staff.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

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ed slide
ed slide
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1 unem 1D
H & E stain
13. Steatosis (assume macro, e.g., large and small droplet)
a. Grade: 0 =<5%; 1 =5-33%; 2 =34-66%; 3 =>66%
b. Location: 0 =Zone 3 (central); 1 =Zone 1 (periportal); 2 =Azonal; 3 =Panacinar
c. Type of macrovesicular steatosis: 0 =Predominantly large droplet; 1 =Mixed large and small droplet;
2=Predominantly small droplet
d. Microvesicular steatosis, contiguous patches: 0 =Absent; 1 =Present
14. Inflammation
a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:
0 =0; 1 =<2 under 20x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag
d. Amount of portal, chronic inflammation: 0=None; 1=Mild; 2=More than mild
d. Fillodik of portal, elifolite ilitalililation. V Trolle, I Trilla, I Trolle than fillia
15. Liver cell injury
a. Ballooning: 0=None → GOTO Item 15d; 1=Few; 2=Many
b. Severe ballooning present: 0 =No; 1 =Yes
c. Classical balloon cells present: 0 =No; 1 =Yes
d. Acidophil bodies: 0 =Rare/absent; 1 =Many
f. Megamitochondria: 0 =Rare/absent; 1 =Many
16. Mallory-Denk bodies: 0 =Rare/absent; 1 =Many
18. Glycogenosis of hepatocytes: 0 =Not present; 1 =Focal, involving less than 50% of the hepatocytes; 2 =Diffuse,
involving greater than or equal to 50% of the hepatocytes
19. Masson's trichrome stain
a. Fibrosis stage: 0=None → GOTO Item 20; 1a=Mild, zone 3 perisinusoidal (requires trichrome);
1b =Moderate, zone 3, perisinusoidal (<i>does not require trichrome</i>); 1c =Portal/periportal only;
2 =Zone 3 and periportal, any combination; 3 =Bridging; 4 =Cirrhosis
b. Perisinusoidal fibrosis grade: 0 =No perisinusoidal fibrosis present; 1 =Perisinusoidal fibrosis present that
requires a Masson stain to identify; 2=Perisinusoidal fibrosis present that is visible on the H&E stain
c. Predominant location of fibrosis: 0 =More predominance around or between portal areas; 1 =No portal or
central predominance; 2 =More predominance around/between central veins
20. Iron stain
a. Hepatocellular iron grade: 0 =Absent or barely discernible, 40x → GOTO item 20c ;
1=Barely discernable granules, 20x; 2=Discrete granules resolved, 10x; 3=Discrete granules resolved, 4x;
4=Masses visible by naked eye
b. Hepatocellular iron distribution: 0=Periportal; 1=Periportal and midzonal; 2=Panacinar; 3=Zone 3 or azonal
c. Nonhepatocellular iron grade: 0=None → GOTO item 21; 1=Mild; 2=More than mild
d. Nonhepatocellular iron distribution: 0 =Large vessel endothelium only; 1 =Portal/fibrosis bands only, but
more than just in large vessel endothelium; 2=Intraparenchymal only; 3=Both portal and intraparenchymal
21. Is this steatohepatitis? 99 =Not NAFLD; 0 =NAFLD, not NASH; 1a =Suspicious/borderline/indeterminate: Zone
3 pattern; 1b =Suspicious/borderline/indeterminate: Zone 1, periportal pattern; 2 =Yes, definite
2 pattern, 22 Suspicious, cordennie, macteriniate. Zone 1, periportar pattern, 2 100, definite
25. Other comments:

NAFLD Database 2

DR - Death Report

Purpose: To record the report of a patient's death.

When: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form whenever the clinical center is informed of a patient's death using as much information about the circumstances of death as possible. Fax a copy of the Death Report (DR) form, including the narrative, and the death certificate (if obtained) to the DCC at (410) 955-0932; Attention: Pat Belt. Also, complete an Interim Event (IE) form and follow the instructions to report a patient's death in the NAFLD Database 2. If either the cause or contributing cause of death is hepatocellular carcinoma (HCC), then also complete an Hepatocellular Carcinoma Report (HC) form.

A. Center, patient, and visit identification					10. Place and location of death		
1. Center ID:				a. Place of death (check only one):			
2. Patient ID:					Hospital	(1)
3. Patient code:					Hospice	(2)
					Home	(3)
4. Date form is init	iated (date of n	iotice):			Nursing home	(4)
day	mon	у	ear		Other (specify):	(₅)
5. Visit code:	_n_		_				
6. Form & revision	:	_dr_	_2	2	Unknown	(6)
7. Study:	NAFLD D	atabase 2	6	6	b. Location of death:	(6)
cuaj.					b. Boomion of down.		
B. Death information	n				city/state/country		
8. Date of death:					11. Has a death certificate been obtained:		
 ,-	_=	=		_	Yes	(No 2)
day	mon	•	ear		If no, please obtain or explain why not:	(2)
9. Source of death		ii that appiy	r):	`			
a. Patient's fami	ıly:		(1)			
b. Friend:			(1)			
c. Other caregiv		NII CDN	(1)			
d. Health care postaff:	rovider or NAS	SH CRN	(1)			
e. Newspaper:			(1)			
f. Funeral parlor	/home:		(1)			
g. Medical recor	·d:		(1)			
h. Medical exan	niner:		(1)			
i. Coroner:			(1)			
j. National Deat	h Index (NDI):		(1)			
k. Social Security (SSDMF):	ty Death Maste	er File	()			
· · · · · · · · · · · · · · · · · · ·	١.		(1)			
1. Other (specify)	/.		(1)			
	other source						
	other source						
	outer source						

12. Underlying cause of death (Study Physician: use whatever knowledge you have to best characterize the primary cause of death); (CHECK ONLY ONE):

011L).	
Coronary heart disease	(01)
Cardiovascular disease	13. (₀₂)
Liver disease	14. (₀₃)
Malignancy (cancer)	15. (₀₄)
Gastrointestinal (GI) disease	16. (₀₅)
Pulmonary (lung) disease	17.
Pneumonia	18.
Complication of diabetes	19. (₀₈)
Accident	19. (₀₉)
	19.
Suicide	19. — 10 <i>)</i>
Homicide	19. — 11)
Kidney disease or renal failure	(12)
Sepsis, staph or other infection	19. (₁₃)
Multi-organ failure	[19.] (₁₄)
Other (specify):	19. (₁₅)
	19.
Unknown	(16)
	19.

Patient I	D#:		
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13. CAUSE OF DEATH: Coronary heart disease (CHD) subclassification (*check only one*): Definite fatal myocardial infarction (MI) or heart attack $\begin{pmatrix} 1 \end{pmatrix}$ 1. Death within 28 days of hospital admission. OR 2. Postmortem findings consistent with MI within 28 days of hospital admission, OR 3. Documented definite or probable MI in previous 28 days if death occurred out of hospital and no evidence of a noncoronary cause of death, OR 4. Autopsy evidence of recent coronary occlusion or MI < 28 days old. Probable fatal MI 2) Defined as: 1. Death within 28 days of hospital admission in cases defined in probable MI cases, **OR** 2. Death within 6 hours of hospital admission with cardiac symptoms and/or signs. Other confirmatory data (biomarkers, ECG) are absent or not diagnostic). Definite fatal CHD $\begin{pmatrix} 3 \end{pmatrix}$ Defined as: 1. A history of CHD and/or documented cardiac pain within 72 hours before death and no evidence of a noncoronary cause of death, **OR** 2. Autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring. Go to 19. 14. CAUSE OF DEATH: Cardiovascular (CVD) disease subclassification (check only one): Congestive heart failure (CHF) 1) Defined as: Death due to clinical, radiologic or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock included). Documented arrhythmia Defined as: Death due to brady- or tachy- arrhythmias not associated with an acute ischemic event.

Defined as: Death due to stroke occurring within 7 days of signs and symptoms of stroke or during

Defined as: Death due to other known vascular diseases including abdominal aortic aneurysm rupture.

Go to 19.

Cerebrovascular (stroke)

admission for stroke.

Other cardiovascular

15. CAUSE OF DEATH: Liver disease subclassification <i>(check only one)</i> :		18.				
Nonalcoholic fatty liver disease				Asthma	(1)
(NAFLD)	(1)		Acute respiratory failure	(2)
Chronic hepatitis C	(2)		Interstitial lung disease (ILD)	(3)
Acute liver failure	(3)		Other (specify):	(4)
Other (specify):	(4)				4)
			19.	Contributing causes of death (check all that apply):		
16. CAUSE OF DEATH: Malignancy (cancer) subclassification <i>(check only one)</i> .	:			a. Coronary heart disease (CHD) (specify).	: (1)
Breast cancer	(01)				
Colon cancer	(02)		b. Cerebrovascular disease (stroke):	(1)
Endometrial/Uterine cancer	(03)		c. Congestive heart failure (CHF):	(1)
Esophageal cancer	(04)		d. Documented arrhythmia, not		
Hepatocellular carcinoma (HCC)* * Complete and key the HC form.	(05)		associated with MI: e. Other cardiovascular disease (specify):	(1)
Ovarian cancer	((60		(2 _F = 250)	(17
Pancreatic cancer	ì	06)				
Prostate cancer	Ì	08)		f. Diabetes Type 1:	(1)
Rectal cancer	(09)		g. Diabetes Type 2:	(1)
Other known cancer or malignant tumor (specify):	(10)		h. Liver disease (specify):	(1)
Unknown cancer site	(₁₁) 		i. Hepatocellular (liver) carcinoma (HCC)*: * Complete and key the HC form.	(1)
17. CAUSE OF DEATH: Gastrointestinal subclassification <i>(check only one)</i> :				j. Other malignancy (cancer) (specify):	(1)
Diverticular disease	()				
Clostridium difficile colitis	$\frac{1}{1}$	1)		k. Gastrointestinal (GI) disease (specify):	(1)
Intestinal obstruction	$\frac{1}{1}$	2 <i>)</i>		\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		12
Ulcer (gastric, duodenal, peptic, gastrojejunal)	(3)		1. Pulmonary (lung) disease (specify):	(
Vascular disorders of the intestine	(₄) ₅)		1. I unifoldity (fullg) disease (specify).	(1)
Other (specify):	(6)				
(-F - 35)	(67		m. Pneumonia:	(1)
				n. Kidney disease:	(1)
19.				o. Sepsis, staph or other infection:	(1)
[19.]				p. Other (specify):	(1)
				q. Unknown:	(<u> </u>
				r. None:	(1))
				1. INOIR.	(1)

20.	Was this a procedure-related death:		
	(Yes 1) [22.	(N	o 2)
21.	Type of procedure-related death (check only one):		
	Cardiac death: Cardiovascular-related procedure (Defined as death after invasive cardiov intervention. Death within 28 days of vascular surgery or within 7 days of cath, arrhythmia ablation, angio	card card	lio- iac
	atherectomy, stent deployment, or other sive coronary vascular intervention.):		
		(1)
	Cardiac death: Noncardiovascular procedure (Defined as cardiac death after noncar cular intervention which occurs within of surgery or other invasive procedure.	28 de	as- ays
	of surgery or other invasive procedure.	· (2)
	Non-cardiac death	(3)
	Unknown	(4)
22.	Was an autopsy performed (check only on	e):	
	Yes	(1)
	No	(2)
	Unknown	(3)
23.	Documentation available for future formal death adjudication (check all that a	ıpply	<i>י</i>):
	a. Medical records documentation:	(1)
	b. Report of autopsy findings:	(1)
	c. Death certificate:	(1)
	d. ER record:	(1)
	e. EMS report:	(1)
	f. Informant interview:	(1)
	g. Coroner's report:	(1)
	h. Other (specify):	(1)
24.	Include a narrative from the Study Physician summarizing the event of death and comorbidities on page 6 and Fax a copy to the DCC ((410) 955-0932; Attention Pat Belt).		
	Narrative is included	(1)
	Narrative is not included	(3)
	If not, please explain why not:	`	2)

- C. Administrative information
- 25. Study Physician PIN:
- **26.** Study Physician signature:
- 27. Clinical Coordinator PIN:
- **28.** Clinical Coordinator signature:
- **29.** Date form reviewed:

day	mon	yea

Narrative - do not key:

FR - FibroScan® Report

NAFLD Database 2

Purpose: To record key data from the FibroScan[®] exam.

When: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

Administered by: NASH CRN certified FibroScan[®] technician(s) and Study Physician.

IMPORTANT: FibroScan[®] examinations may only be performed on NASH CRN patients. DO NOT perform on non-NASH CRN patients, per agreement with manufacturer.

Instructions: Verify that the patient has understood and signed the FibroScan consent form then file a copy in the patient records. Perform the exam per the procedures in the NAFLD Adult Database 2 SOP I. Briefly, this involves the following:

Before FibroScan examination, review the following information with patients: 1) Patients must have fasted for three or more hours prior to the FibroScan procedure (necessary medications are allowed with small amounts of water). 2) Clothing must permit access to the abdomen. 3) Check that the patient has no FibroScan contraindications (see item 9).

Instructions for keying data on FibroScan Touch Screen

1) On the FibroScan device, enter the patient ID (e.g., 9999) in the **LASTNAME** field; enter the letter code (e.g., zyx) in the **FIRSTNAME** field, and enter the visit code followed by NASH in the **CODE** field (e.g., t0 NASH). Enter NAFLD in the **ADMITTING DIAGNOSIS** field. Enter the PIN number of certified technician in the **OPERATOR** field.

Conduct of the two required FibroScan® procedures:

- 1) Emphasize the need to remain still during the procedure. 2) Position patient supine with right arm raised behind his/her head. 3) Apply a dime-sized amount of water based conduction gel over the liver. 4) Place M or XL probe over liver and obtain 10 valid measurements (if necessary, repeat until you have 10 valid measurements).
- 5) To choose between M and XL probe, follow the recommendation provided by the device. In case of recommendation fluctuating between M and XL, choose the XL. 6) Save test results, print test report, record results in Section D. 7) Repeat steps 2-6 above for second FibroScan exam. Each patient will have two exams. Reminder: Exam #2 may be performed by the same technician who completed Exam #1 or by a different certified technician.
- 8) Record results from the second exam in Section E.

A. Center, patient, and visit identification

1. Center ID:			
2. Patient ID:			
3. Patient code:			
4. Date form completed	(date of FibroS	can® e	exam):
	mon		ear
5. Visit code:			
6. Form & revision:	<u>f</u>	<u>r</u>	_5_
7. Study:	NAFLD Datab		6

B. Consent

- 8. Has the patient signed the FibroScan® consent:

 Yes

 (*
 1)

 21.
 - * A FibroScan[®] exam should not be performed unless consent is obtained.
- **9.** Does the patient have any of the following contraindications (check all that apply):
 - **a.** An active implant such as pacemaker, defibrillator, pump, etc.: $\binom{}{}$
 - **b.** Wound near the site of scan: $\binom{1}{1}$
 - **c.** Pregnancy: (1)
 - **d.** Ascites (fluid in the abdomen):
 - **e.** Patient did not fast for 3 hours: $\binom{1}{2}$
 - **f.** Were any of the items above (a-e) checked:

Yes	No
(* 1)	(2)
21.	_
	6

* If any of the above are checked, the FibroScan[®] exam SHOULD NOT be performed. Skip to item 21.

C. FibroScan® Procedure information	n	E. F	ibroScan [®] exam #2 results	
10. Was FibroScan [®] exam performed:			(This may be done by the san	ne technician or a
Y			different technician).	
((es	17.	FibroScan® Technician PIN:	
12.	J			
* Complete item 11, then skip to it	em 21.	18.	Number of measurements	
11. Reason FibroScan® exam not perform (check all that apply):	ormed		a. Valid measurements*:	# of valid measurements
a. Patient had a skin-to-capsule dis measurement greater than 3.5cm			b. Invalid measurements:	# of invalid measurements
b. Other (specify):	(1)		c. Total measurements:	# of total measurements
Skip to item 21.			To calculate invalid measu valid measurements from total	
•			* Note: at least ten valid measu	arements should be
12. Probe type used:			made.	
M:	(1)	10	Equivalent Liver Stiffness (E)	
XL:	(2)	10.	a. Median (kPa):	•
D. FibroScan® exam #1 results			a. Median (Kra).	(1.5-75.0)
D. FibroScan exam #1 results			b. IQR (kPa):	•
13. FibroScan [®] Technician PIN:			b. Test (ki a).	
			c. IQR/med:	
14. Number of measurements				%
a. Valid measurements*:		20.	Controlled Attenuation Parame	ter (CAP)
•	# of valid measuremen	nts	a. Median (dB/m):	
b. Invalid measurements:				(100-400)
#	of invalid measureme	ents	b. IQR (dB/m):	
c. Total measurements:			Di iqir (az/m)	
	# of total measuremen		dministrative information	
To calculate invalid measuren valid measurements from total me		г. А	duministi ative inivi mativi	
* Note: at least ten valid measurer made.		21.	Study Physician PIN:	
		22.	Study Physician signature:	
15. Equivalent Liver Stiffness (E)				
a. Median (kPa):	<u> </u>			
	1.5-75.0)	23	Clinical Coordinator PIN:	
b. IQR (kPa):	<u> </u>	20.	omital coordinator ray.	
		24.	Clinical Coordinator signature:	
c. IQR/med:			· ·	
16. Controlled Attenuation Parameter	(CAP)	25	Date form reviewed:	
a. Median (dB/m):	(100,400)	~ U.		_
	(100-400)		day mon	year
b. IQR (dB/m):				

FLINT

MR - MRI Consent and Report Form

Purpose: To document the collection and transmittal of MRI data.

When: Visit s and f72.

By whom: Study Radiologist/Study Physician and Clinical Coordinator.

Instructions: Complete this form based on the consent documents signed by the patient. Patient may still participate in FLINT trial without an MRI. Please consult FLINT SOP VI for additional procedures.

Before MRI examination review the following basic information with subjects: 1) Subjects should fast for four or more hours if possible before the MRI examination. 2) Necessary medications are allowed with small amounts of water. 3) Rehearse breathing instructions with subject. Subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and to reduce discomfort associated with breath-holding. 4) Explain the necessity of remaining still during the MRI examination.

On day of MRI examination confirm the following information with subjects: 1) Subject identity. 2) MRI consent is signed and a copy of consent kept on site. 3) No MRI contraindications. 4) Emptied bladder prior to scanning. 5) Subject has been weighed, and been asked height. 6) MRI-compatible clothing (no metal or metallic/shiny clothing). 7) Breathing instructions rehearsed and understood (subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and reduce discomfort associated with breath-holding).

Pre-MRI preparation: 1) Subjects to be positioned supine. 2) Ensure subject comfortable on scanner table. 3) For 3T MRIs, place dielectric pad over liver. 4) Place phased-array coil (over dielectric pad, for 3T scanners) centered over the liver; ensure good connection to scanner.

A. Center, patient and visit identification

- 1. Center ID:
- **2.** Patient ID: ____ ___ ____
- **3.** Patient code: _____ ____
- 4. Date form completed:

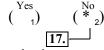
day mon year

- **5.** Visit code: ____ ___
- **6.** Form & revision: __m__r__1__
- **7.** Study: FLINT _7_
- **8.** Is FLINT MRI protocol currently in use at your center:



B. Consent

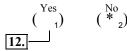
9. Has the patient signed the FLINT MRI consent:



* An MRI should not be performed unless consent is obtained.

C. MRI results and information

10. Was an MRI performed:



- * Complete item 11, then skip to item 17.
- **11.** Reason MRI not performed *(check all that apply)*
 - a. Patient was not fasting:
 - **b.** Patient suffers from extreme claustrophobia:
 - c. Patients weight or girth exceeds MRI scanner capabilities:
 - **d.** Other (specify):

		17.
12.	Technician name:	

print name

13. Date and time of MRI:

_	day	mon	year
a. Time:	,		,
	:	() ()
hour	minute	– \ am) (₂ , pm

- **14.** Dates images sent to MRI Reading Center
 - a. By CD/DVD:

day mon year

b. By secure in-server connection (enter "m" if not available):

day mon year

- D. Administrative information
- **15.** Study Radiologist or Study Physician PIN:

16. Study Radiologist or Study Physician signature:

17. Clinical Coordinator PIN: ____ __

18. Clinical Coordinator signature:

19. Date form reviewed:

day mon year

NAFLD Database 2

HC - Hepatocellular Carcinoma Report

Purpose: To record the report of a patient's diagnosis of hepatocellular carcinoma (HCC).

When: As soon as clinic is notified of a patient's diagnosis of HCC.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form whenever the clinical center is informed of a patient's diagnosis of HCC. Fax a copy of the Hepatocellular Carcinoma Report (HC) form to the DCC at (410) 955-0932; Attention: Pat Belt. Also, complete an Interim Event (IE) form to report a patient's HCC diagnosis in the NAFLD Database 2.

A. Center, patient, and visit identification

- 1. Center ID:
- 2. Patient ID:
- 3. Patient code:
- **4.** Date form initiated (date of notice):

_		_
day	mon	year

- **5.** Visit code:
- **6.** Form & revision:
- <u>h</u> <u>c</u> <u>1</u>

- 7. Study:
- NAFLD Database 2 6

B. Diagnosis information

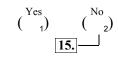
8. Date of diagnosis:

<u>=_</u>		<u> </u>
day	mon	year

- **9.** How was HCC identified (check all that apply):
 - a. Ultrasound: **b.** CT scan:

 - c. MRI: **d.** Biopsy:
 - e. Other (specify):

10. Were results of imaging obtained:



11. Were multiple tumors identified:

12. Size of tumor (enter size of largest tumor if more than one):

	cm	1	

13. Was early enhancement present:



14. Was delayed washout present:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

15. Was serum marker alfa fetoprotein (AFP) obtained:



- a. Was serum AFP elevated:
- **b.** Serum AFP level:

0.0 ng/mL -	2999.9 ng/mL

C. Administrative information

- 16. Study Physician PIN:
- 17. Study Physician signature:
- 18. Clinical Coordinator PIN:
- 19. Clinical Coordinator signature:
- **20.** Date form reviewed:



NAFLD Database 2

IE - Interim Event Report

Purpose: To document events that occur after registration that impact on the patient's participation in the NAFLD Database 2 Study (eg, mild or moderate liver biopsy complications). Complete this form if there has been an incident cirrhosis, hepatocellular carcinoma (HCC), hospitalization, Emergency Room visit, liver transplant, an event associated with a study-related procedure, or death.

When: As needed; use visit code n. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code n for first event, n1 for second event, etc.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 16) and the severity code (item 17) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at https://jhuccs1.us/nash/default.asp. Click on Documents and then click on General Documents. Fax the DCC (Attention: Pat Belt) a copy of this form if severity grade is 3 or higher (Fax 410-955- 0932).

NASH CRN Data Coordinating Center telephone number: (410) 955-8175.

A. Center, patient, and	l visit identificat	ion	C. Patient information			
1. Center ID:			9. Date enrolled in NAFLD Study (enter n if patient i		led):	
2. Patient ID:						
			day	mon	year	
3. Patient code:			10. Gender:			
4. Date of report:			Male		(1.
2. Date of report.			Female		(2,
day	mon	year	11. Age at time of event:			
5. Visit code:			11. Age at time of event.	_	years	
3. Visit code.	_n		D. Event description			
6. Form & revision:	_i_	e3_	12. Date event started:			
7. Study:	NAFLD Datal	pase 2 <u>6</u>			year	
3. Visit interval identi	fication		13. Nature of event (check al	l that apply)		
			a. General anesthesia		(1/
8. Most recently com or follow-up)	pleted visit (scree	ening	b. Study-related procedure	re:	(1/
a. Date:			c. Drug interactions:		(14
		_=	d. Worsening of a co-mo	rbid illness:	(1-
day	mon	year	e. Hypoglycemia:		(1.
b. Visit code:			f. New-onset diabetes:		(1
			g. Pregnancy (patient):		(1/
			h. Cirrhosis:		(1/
			i. Hepatocellular carcino. * Complete and key the	ma (HCC):	(*	: \ 1 [,]
			Complete and key the	: IIC 101 III.		

14. Did the event lead to (check all that apply,a. Emergency room visit:) (1)	18.		ent resolved if event is not	yet resolved):	
b. Hospitalization:	(1)					
c. Infectious episode:	(1)			day	mon	year
d. Surgical intervention:	(1)	19.	What ac	tion was taken	:	
15. Describe event:							
			90	Otheres	ammonts on our	onti	
			ZU.	Otner co	omments on eve	ent:	
16. Is the event listed in the NCIs Common							
Terminology Criteria for Adverse Events (CTCAE v3.0 document available at https://jhuccs1.us/nash/default.asp; click on Documents and then click on General							
Documents): ${{\operatorname{Yes}}\choose{{}^{1}}}$	(No 2)					
a. Indicate the name of the event (if in the CTCAE, specify name exactly from document; if not in CTCAE specify name):			F. A	dministr	ative informa	tion	
			21.	Clinical	Coordinator P	IN:	
			22.	Clinical	Coordinator si	gnature:	
17. Indicate the severity code using the CTCAE grading scale for the AE specified (severity grades are listed in the CTCAE v3.0 document availahttps://jhuccs1.us/nash/default.asp; c	b l e		23.	Study Pl	hysician PIN:		
Documents and then click on General ments):			2.4	Study Pl	nysician signat	iire.	
Grade 1 - Mild	(1)	~ 4.		J >===== 0.8.iut		
Grade 2 - Moderate	(2)					
Grade 3 - Severe†	(2' 3)	95	Data for	m reviewed:		
Grade 4 - Life threatening or disabling†	(4)	٤J.	Date 101	m ievieweu.		
Grade 5 - Death†	(* 5)			day	mon	year
† Fax the DCC (Attention Pat Belt) a copy of this form if severity grade is 3 or high		(Fax			s form and fax copy of this for		

Key this form and fax the DCC (Attention: Pat Belt) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious events so that we assure appropriate and timely study wide review. The received reports will be reviewed by Jeanne Clark, the Safety Officer, for appropriate further review by the Steering Committee and Data and Safety Monitoring Board.

410-955-0932).

*Complete and key Death Report (DR) form.

IE - Interim Event Report

Purpose: To document an adverse event that threatens the integrity of the FLINT trial or well-being of a study participant that includes, but not limited to:

- (1) events that impact the patient's treatment or participation in FLINT
- (2) adverse events that are recorded on the Follow-Up Medical History (HI) form
- (3) adverse events that may or may not be related to study drug
- (4) other events that clinical center staff feel should be reported
- (5) when a follow-up report is needed for a previously completed IE form

As defined by Title 21 Code of Federal Regulations Part 312.32 IND Safety Reporting:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other medical events may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

When: As needed. Use visit code if reporting an event discovered during a regular follow-up visit. Use visit code n if event is discovered between study visits. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code for first event, n for second event, n2 for third event, etc. Adverse events that are serious, unexpected and have reasonable possibility of being caused by FLINT study drug should also be recorded on the Serious Adverse Event/IND Safety Report (SR) form.

Completed by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 16) and the severity grade (item 17) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Studies and then FLINT. Fax the DCC (Fax 410-955-0932; Attention: Ivana Vaughn) a copy of this form if severity grade is 3 or higher within 1 week for further review by Dr. Jeanne Clark, the NASH CRN Safety Officer. For more information, see SOP I sections 6.15 and 6.16.

Follow-up report: A follow-up report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patient's condition or in the physician's judgment about the event since the previous report was filed.

A. Center, patient, and visit identification		5. Visit code: if report not associated with a visit, fill in "n"				
1. Center ID:						
		6. Form & revision:	<u>i e 3</u>			
2. Patient ID:		- 0. 1	FLINT 7			
2 P. C. 1		7. Study:	TLINI _/_			
3. Patient code:						
4. Date of report:						
day	mon year					

B. Visit interval identification			14. Describe event:		
8. Most recently completed visit (screening or followup)					
a. Date:	year				
b. Visit code:					
C. Patient information					
9. Gender:			For items 15, 16, and 17, please refer to CTC available at www.nashcrn.com; click on Stud		
Male	(1)	then FLINT.	es un	и
Female	(2)	15. Identify body system (check all that app	lv)	
10. Age at time of event:			a. Auditory/ear:	(1)
Ç	years		b. Allergy/immunologic:	(.)
D. Event description			c. Ocular/visual:	(1)
11. Is this the first report or a followup report			d. Hepatobiliary/pancreatic:	(1)
for this adverse event:			e. Infection:	(1)
First report	(1)	f. Constitutional symptoms:	(1)
Followup report	(2)	g. Psychiatric:	(1)
12. Date event started:			h. Cardiovascular:	(1)
			i. Dermatologic/skin:	(1)
day mon	year		j. Endocrine/metabolic:	(1)
13. Nature of event (<i>check all that apply</i>)			k. Gastrointestinal/digestive:	(1)
a. Drug dispensing mixup:	(1)	l. Lymphatic/blood:	(1)
b. Medication related event:	(1)	m. Musculoskeletal:	(1)
c. Study procedure related event:	(1)	n. Neurologic:	(1)
d. Severe allergic reaction:	(1)	o. Pulmonary/respiratory:	(1)
e. Drug interactions:	(1)	p. Renal/genitourinary:	(1)
f. Worsening of a co-morbid illness:	(1)	q. Sexual/reproductive:	(1)
g. Patient reported symptom of hepatotoxicity:	(1)	r. Other (specify):	(1)
h. Hypoglycemia/hyperglycemia:	(1)	specify other body system		
i. Diabetes:	(1)	s. None of the above:	(1)
j. Pregnancy (patient):	(*1)		`	1/
k. Other (specify):	(1)	16. Short name for event if applicable:		
			Not applicable	(0)

^{*}FLINT study drug will be discontinued if a patient becomes pregnant. Contact the NASH CRN Data Coordinating Center to unmask the study drug.

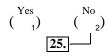
17.	Severity grade:		
	Not an adverse event		(0)
	Grade 1 - Mild		(1)
	Grade 2 - Moderate		(2)
	Grade 3 - Severe		(3)
	Grade 4 - Life threaten	ing or disabling	(4)
	Grade 5 - Death		(* 5)
	*Complete and key De	ath Report (DR) f	form.
18.	Randomization in FLIN	NT	
	a. Has patient been ran FLINT:	domized in	
		Yes	No
		· _	(₂)
	b. Date randomized in		26.
	day	mon	year
19.	Is the patient currently FLINT study drug:	receiving the	
		Yes	No
		(₁)	(₂)
20.	Patient's history of trea FLINT study drug	tment with	
	a. How long has patier drug:	nt been on study	
	b. Have there been any interruptions or resta		
		Yes	(No
	Include stop/restart	dates and reason	s: 2)
21.	Is there evidence to sug relationship between th drug and the adverse ev	e FLINT study	
	Definitely yes		(1)
	Probably yes		(2)
	Possibly yes		(3)
	Probably no		(4)

22.	Is	this	a	serious	adverse	event:

Y	es	No
(1)	(2)
		23.

If Yes, then select all the reasons that apply:

- **a.** Severity Grade 4 or 5:
- **b.** Required inpatient hospitalization or prolonged existing hospitalization: (1)
- c. Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions:
- **d.** Jeopardized patient and required medical or surgical intervention to prevent a serious event:
- e. Congenital abnormality or birth defect: (1
- 23. Is this an unexpected adverse event:



24. Reason the adverse event was unexpected:

Not listed in the obeticholic acid investigator's brochure (1)

Listed in the obeticholic acid investigator's brochure, but not at the specificity or severity that has been observed

verity that has been
(2)
eticholic acid

Listed in the obeticholic acid investigator's brochure as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with previous experience of obeticholic acid

25. Did you select "Yes" for items 21 (definitely, probably, or possibly), 22, and 23:

Yes (No (No (2))

*If Yes, please also complete a Serious Adverse Event/IND Safety Report (SR) form and follow instructions.

26. Current status of adverse event (check only one):

Resolved	(1
Active	(2
Unknown	28. (₃
	28

Definitely no

Patient ID:		

27. Date adverse event resolved:				E. Administrative information		
	day	mon	year	30. Clinical Coordinator PIN:		
28. What	t action was take	n:		31. Clinical Coordinator signature:		
_				32. Study Physician PIN:		
_				33. Study Physician signature:		
29. Othe	Other comments on event:			34. Date form reviewed:		
				day mon year		
				Key this form and fax the DCC (Attention: Ivand Vaughn) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious adverse events so that we assure appropriate and timely study wide review. The serious adverse event reports will be reviewed by Dr. Jeanne Clark, the Safety Officer.		

SR - Serious Adverse Event/IND Safety Report

Purpose: To report serious adverse events recorded on the Interim Event Report (IE) form that satisfy the FDA expedited FDA Safety Report requirements outlined in the FLINT Trial protocol. In order to satisfy FDA expedited IND Safety Report requirements the event must be SERIOUS, UNEXPECTED, AND have a REASONABLE POSSIBILITY of being caused by FLINT study drug, as defined by Title 21 Code of Federal Regulations Part 312.32 IND Safety Reporting:

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "SERIOUS" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "REASONABLE POSSIBILITY" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "**UNEXPECTED**" if it is not listed in the obeticholic acid investigator's brochure or is not listed at the specificity or severity that has been observed for your patient.

When: The SR form should be used only for reporting a serious and unexpected adverse event which meets the IND Safety Report criteria as stated above, or when a followup report is needed for a previously completed SR form. When the serious adverse event does not meet the expedited IND Safety Report criteria, use the Interim Event Report (IE) form to report the event.

Completed by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form **within 2 business days**. The short name (item 24) and the severity grade (item 25) are to be obtained from the NCIs Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. (Click on Studies then click on FLINT). Report the serious advere event to your IRB per local guidelines. Send the Data Coordinating Center the following:

- 1) A copy of this SR form and corresponding IE form
- 2) A narrative description of the event that includes all of the information provided on the SR and IE forms and a justification of why the event is serious, unexpected and has reasonable possibility of being caused by FLINT study drug (see FLINT SOP I, section 6.16).
- 3) A copy of your report to your IRB, if applicable

The Data Coordinating Center will submit a preliminary copy of the report to NIDDK (Sponsor) for further review within 3 business days. If NIDDK staff determines that an expedited IND Safety Report is required, a final report will be submitted to the FDA (within 15 days). Intercept Pharmaceuticals (manufacturer of study drug), the DSMB, and Steering Committee will be notified of all serious adverse events requiring an expedited IND safety report within 7 days of keying the SR form. For more information, see FLINT SOP I, section 6.16.

Followup report: A followup report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patients condition or in the physicians judgment about the event since the previous report was filed.

A. Center, patient and	visit identification	4. Date of report:		
1. Center ID:				year
2. Patient ID:		5. Visit code: If report not associate	d with a visit, fil	l in ''n.''
3. Patient code:		6. Form & revision:	_S_	_r3_
		7. Study:	FL	INT <u>7</u>

1)

B. Participant information

8. Date randomized in FLINT:

day	mon	year

9. Gender:

Male	(1)
Female	(2)

10. Age at time of adverse event:

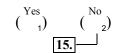
years

C. Determination of an serious adverse report

11. Is there evidence to suggest a causal relationship between FLINT study drug and the adverse event:

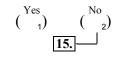
Definitely yes	(1)
Probably yes	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
Possibly yes	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
Probably no	(4)
Definitely no	15

12. Is this a serious adverse event:



If Yes, then select all the reasons that apply:

- **a.** Severity Grade 4 or 5:
- **b.** Required inpatient hospitalization or prolonged existing hospitalization: (1)
- c. Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions: (1)
- e. Congenital abnormality or birth defect: (
- 13. Is this an unexpected adverse event:



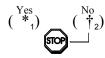
14. Reason the adverse event was unexpected:

Not listed in the obeticholic acid investigator brochure

Listed in the obeticholic acid investigator's brochure, but not at the specificity or severity that has been observed

Listed in the obeticholic acid investigator's brochure as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with previous experience of obeticholic acid (

15. Did you select "Yes" for items 11, 12, and 13:



*NIDDK will determine if an expedited IND Safety Report will be submitted to the FDA within 15 calendar days.

†Use FLINT forms HI and IE to report adverse events that are not serious, not associated with the FLINT study drug, or are expected. Do not key this form.

D. Serious adverse event description

16. Is this the first report or a followup report for this serious adverse event:

First report

Followup report (2

17. Date of serious adverse event onset:



18. Date serious adverse event was reported to clinical center:

_		=
day	mon	year

19. Describe the serious adverse event:

	FLINT stu		nents other than se at the time of	
21.	Specify tes comorbidit	sts/treatments ties:	s and	
22.	Was an uns	scheduled liv	ver biopsy	
	performed:		$\begin{pmatrix} \text{Yes} \\ * \\ 1 \end{pmatrix}$	No
		copy of the it he SR form.	nstitutional pathol	
23.	Did the ser significant		e event result in	(No 2)
	Specify:		<u>2</u>	4. — "
24.	(short nam CTCAE v3 at www.na	nes for AEs a 3.0 document	click on Studies	

25. Severity grade (severity grades are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Studies and then click on FLINT):

Grade 3 - Severe (1)

Grade 4 - Life threatening or

disabling (2
Grade 5 - Death (*2

*Complete and key the Death Report (DR) form.

26. Current status of serious adverse event *(check only one):*

Resolved (1)
Active (2)
Unknown (3)

27. Date resolved:

day mon year

28. Additional comments on serious adverse event:

17	A .1	:_	•	4:	: C	mation
н	An	mın	istra	tive	intor	mation

29.	Study Physician PIN:		
30.	Study Physician signature:		
31.	Clinical Coordinator PIN:		
32.	Clinical Coordinator signature:		
33.	Date form reviewed:	_	

Key this form and send the DCC within 2 business days:

mon

year

- (1) A copy of this SR form(2) A narrative description of the serious adverse event
- (3) A copy of your report to your IRB.

We are asking for copies of these reports on serious adverse events so that we assure appropriate and timely study wide review. The serious adverse event report will be reviewed by Dr. Jeanne Clark, the Safety Officer, and NIDDK (Sponsor).

BG - Baseline History

Purpose : To collect baselin When : Visit t0.	e history information about the	e patient.		
	Coordinator, reviewed by Stud	ly Physician.		
agrees with the diagnosis the patient is ineligible ar data system; but the form	nation by interview and chart r, the patient is ineligible for the ad cannot enroll in the NAFLD	review. If cis checked for an item, and the physic NAFLD Database 2 Study. If sis checked for a Database 2 Study. The form should not be keyed as for other patients who started screening, but were	an ite to th	em, ne
to be ineligible.				
A. Center, visit, and pat	ient identification	9. If yes, characterize the liver disease(s) <i>(check all that apply)</i>		
1. Center ID:		a. Alcohol related liver disease:	(1)
2. Patient ID:		b. Viral hepatitis:	(1)
_, _ , _ , _ ,	<u> </u>	c. Alpha-1 antitrypsin deficiency:	(1)
3. Patient code:		d. Wilson's disease:	(1)
		e. Glycogen storage disease:	(1)
4. Visit date (date this for	orm is initiated):	f. Iron overload:	(1)
	mon year	g. Fatty liver disease (NAFLD, NASH):	(1)
·	, and the second	h. Type of liver disease unknown:	(1)
5. Visit code:	_t0	i. Other (specify):	(1)
6. Form & revision:	_bg2_	specify		
7. Study:	NAFLD Database 2 6			
B. Family history	<u>-</u>	10. Do/did any of the patient's first degree relatives (parent, brother, sister, child) have cirrhosis:		
8. Do/did any of the pat relatives (parent, brothave liver disease:		$\binom{\text{Yes}}{1}$	(¹	No _2)
Did any of the most	$ (\begin{matrix} \text{Yes} \\ 1 \end{matrix}) \qquad (\begin{matrix} \text{No} \\ 2 \end{matrix}) $	11. If yes, is the cause of the cirrhosis NASH-related or unknown (cryptogenic): (Yes (1)		No 、
a. Did any of the pati relatives die from		(₁)	(2)
	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	12. Do any of the patient's first degree relatives (parent, brother, sister, child) have diabetes (Type 1 or Type 2):		
		Yes	(1)
		No	(2)
		Don't know	(3)
		13. Do any of the patient's first degree relatives (parent, brother, sister, child) have obesity:		
		Yes	(1)
		No	(2)
		Don't know	(3)

Patient		

14.	Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:			19. Does the patient have a liver biopsy done no more than 90 days prior to registration in the Database 2 Study that you want
	Yes	(1)	evaluated for the Database 2 Study (complete the Liver Biopsy Histology Findings (HF) and Liver
	No	(2)	Biopsy Materials Documentation (SD) forms for
	Don't know	(3)	this biopsy):
15	Do any of the nations's first degree			$\binom{\text{Yes}}{*}$ $\binom{\text{No}}{2}$
13.	Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood			*Blood drawn for specimen collection must be
	fat:	,		within 90 days of the biopsy.
	Yes	(1)	20 D (Cl' 1')
	No	(2)	20. Date of liver biopsy no more than 90 days prior to registration in Database 2
	Don't know	(3)	Study that you want evaluated:
C. I	NAFLD history			
16.	Date patient was first diagnosed with			day mon year
10.	fatty liver disease or NASH-related cirrhosis:			21. Will the patient have a biopsy during screening:
		_		$\binom{\text{Yes}}{*}_{1}$ $\binom{\text{No}}{2}$
	day mon y	/ear		
17.	What prompted the evaluation for NAFLD, NASH, or NASH-related cirrhosis (check all that apply)			*Complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy. Blood draw for banking should be done <u>prior</u> to the biopsy or 4 days
	a. Symptoms for liver disease:	(1)	after the biopsy.
	b. Result of being evaluated for another illness:	(1)	22. Has the patient had a liver imaging study in the past 6 months:
	c. During a routine or insurance physical			$\begin{pmatrix} \text{Yes} & \text{No} \\ \begin{pmatrix} * \\ 1 \end{pmatrix} & \begin{pmatrix} \text{No} \\ 2 \end{pmatrix} \end{pmatrix}$
	examination:	(1)	$\binom{1}{1}$ $\binom{2}{2}$
	d. Blood donation:	(1)	*Complete the Liver Imaging Studies Report (IR) form.
	e. Other (specify):	(1)	jorni.
				D. Weight history
	specify			22. What was the nationt's hirthwaight:
40				23. What was the patient's birthweight:
18.	What procedures/tests supported this first diagnosis (check all that apply)			lbs oz
	a. Liver biopsy:	(1)	24. Review flashcard 11. Which (picture)
	b. Imaging studies (Ultrasound, CT, MRI).	: (1)	best describes your weight pattern over
	c. Elevated aminotransferases:	(1)	the past 5 years (check only one):
	d. Other (specify):	(1)	Up and down, up and down
	· - · · · · · · · · · · · · · · · · · ·	`	12	Up gradually (2)
	specify			Up sharply (gained a lot in a brief interval) $\binom{3}{3}$
				Down gradually (4)
				Down sharply (lost a lot in a brief interval) $\binom{5}{5}$
				No or minimal change ()

25. What is the patient's current weight (ask the patient for his/her weight):

lbs

35. Did the patient try to lose or gain weight:

26. What is the most the patient has ever weighed:

Gain weight Lose weight

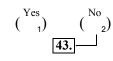
27. At what age did the patient weigh the

E. Tobacco cigarette smoking history (interview with patient; not interview with parent, not by chart review)

36. Which did the patient try to do (check only one):

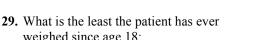
most:

37. Is the patient age 12 or older:



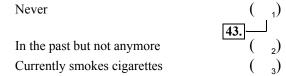
28. Is the patient age 18 or older:

38. Have you ever smoked tobacco cigarettes:



lbs

age in years



30. At what age did the patient weigh the

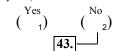
weighed since age 18:

least since age 18:

39. Did you smoke cigarettes regularly ("No" means less than 20 packs of cigarettes in a lifetime or less than I cigarette a day for one year):

age in years

lbs



years

years

31. Does the patient weigh more than he/she did one year ago:

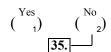
40. How old were you when you first started regular cigarette smoking:

32. How much more does the patient weigh now compared to one year ago:

41. How old were you when you (last) stopped smoking cigarettes (code as "n" if the patient didn't stop smoking):

33. Does the patient weigh less than he/she did one year ago:

42. On the average of the entire time that you smoked cigarettes, how many cigarettes



lbs

did you smoke per day:

34.	How much less does the patient weig	h
	now compared to one year ago:	

cigarettes/day

F. Menstrual history

43. Is the patient female:

Yes	No .
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	49.

44. Has menarche occurred:

(Ye	es 1)		(No (
	.,	49.	_	_ ً

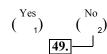
45. If yes, what was the patient's age at menarche:

age in years

46. Characterize the menstrual history in the past 5 years *(check only one):*

Regular periods	(1)
Irregular periods	(2)
Rare periods	(3)
No periods	(4)

47. Is patient post-menopausal:



48. What was the patient's age at menopause:

age in years

- G. Medical history (means Caution; condition is exclusionary if study physician agrees with diagnosis)
- **49.** Has the patient ever been diagnosed with and treated for any of the following (check all that apply; source of information can be interview and/or chart review)
 - **a.** Diabetes type 1:
 - **b.** Diabetes type 2:
 - **c.** Gestational diabetes (diabetes of pregnancy):
 - d. Hepatitis B:
 - e. Hepatitis C:

- **f.** Autoimmune hepatitis:
- g. Autoimmune cholestatic liver disorder (PBC or PSC):
- h. Wilson's disease:
- i. Alpha-1-antitrypsin (A1AT) deficiency: (1)
- j. Glycogen storage disease:
- k. Iron overload:
- **I.** Polycystic liver disease: (1)
- **m.** Drug induced liver disease:
- **n.** Gilbert's syndrome:
- **o.** Esophageal or gastric varices on endoscopy:
- **p.** Bleeding from varices: (1)
- **q.** Other gastrointestinal bleeding: (1)
- r. Ascites:
- s. Edema:
- **t.** Hepatic encephalopathy:
- u. Portal hypertension:
- v. Hepatorenal syndrome:
- w. Hepatopulmonary syndrome:
- **x.** Short bowel syndrome: (1)
- x. Short bower syndrome.
- y. Hemophilia (bleeding disorder):
- z. HIV positive:
- aa. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:
- **ab.** Endocrine disease *(hormonal abnormality):* (1)
- ac. Hepatocellular carcinoma:
- ad. Other malignancy (cancer):
- **ae.** Peripheral neuropathy: (1)

	af. Seizure disorder or epilepsy:	(1)	51. Organ, limb, or bone marrow transplan
	ag. Drug allergies:	(1)	a. Has the patient ever received a liver
	ah. Hypothyroidism:	(1)	transplant: Yes
	ai. Hypertension:	(1)	(1)
	aj. Cerebrovascular disease:	(1)	b. Has the patient ever received any other organ, limb, or bone marrow
	ak. Dysbetalipoproteinemia:	_ (ı	1)	transplant:
		/C_			$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix}$
	al. Chronic cholestasis:	(1)	52. Has the nationt received total perentare
	am. Hyperlipidemia (high cholesterol, high triglycerides):	(1)	52. Has the patient received total parentera nutrition (TPN) for more than 1 month within 6 months prior to liver biopsy:
	an. Pancreatitis:	(1)	Yes
	ao. Cholelithiasis:	(1)	(1)
	ap. Coronary artery disease:	(1)	,
	aq. Elevated uric acid such as gout:	(1)	53. Is the patient currently undergoing
	ar. Kidney disease:	(1)	evaluation for bariatric surgery:
	as. Polycystic ovary syndrome:	(1)	$\begin{pmatrix} 1 & 1 \\ 1 \end{pmatrix}$
	at. Sleep apnea (not breathing during sleep):	(1)	54. Does the patient have symptoms suggestive of sleep apnea <i>(snoring,</i>
	au. Dermatologic disorders:	(1)	observed periods of apnea, disruptive
	av. Myopathy:	(1)	sleep disturbances): Yes
	aw. Myositis:	(1)	(1)
	ax. Major depression:	(1)	
	ay. Schizophrenia:	(1)	
	az. Bipolar disorder:	(1)	
	ba. Obsessive compulsive disorder:	(1)	
	bb. Severe anxiety or personality disorder:	(1)	
	bc. None of the above:	(1)	
50.	Has the patient ever had surgery for an of the following (check all that apply)	у			
	a. Stapling or banding of the stomach:	<u>(c)</u>		1)	
	b. Jejunoileal <i>(or other intestinal)</i> byp prior to the diagnosis of NAFLD:	ass (1)	
	c. Biliopancreatic diversion:	<u>(c)</u>		1)	
	d. Other GI or bariatric surgery (specified)	fy): (1)	

e. None of the above:

(1)

H. Medication use

Glynase):

g. Insulin:

55. Has the patient used any antidiabetic medications in the past 3 months:

	$\binom{\text{res}}{1}$	(NO) 2)
	56.		
(If yes, check all that apply):			
a. Acarbose (Precose):		(1)
b. Acetohexamide (Dymelor):		(1)
c. Chlorpropamide (Diabinese):		(1)
d. Glimepiride (Amaryl):		(1)
e. Glipizide (Glucotrol, Glucotr	ol XL):	(1)
f. Glyburide (Micronase, DiaBe	eta.		

- **h.** Metformin (Glucophage, Glucophage XR): (
- i. Miglitol (Glycet): (j. Nateglinide (Starlix): (
- j. Nateglinide (Starlix):

 k. Pioglitazone (Actos):

 (1)
- I. Repaglinide (Prandin):
- **m.** Rosiglitazone (Avandia): $\binom{1}{1}$
- n. Tolazamide (Tolinase): (1)o. Tolbutamide (Orinase): (1)
- **p.** Other, (*specify*): (1)
- **56.** Has the patient taken any alcohol abuse (dependance or withdrawal) medications in the past 3 months:

Y	es		(N	No ,
(1)		(2)
		57.		J

1)

(If yes, check all that apply):

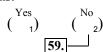
- **a.** Chlordiazepoxide (Librium): $\binom{1}{1}$
- **b.** Clorazepate dipotassium (Tranxene): (1)
- c. Diazepam (Valium): (1)
- **d.** Disulfiram (Antabuse):
- e. Hydroxyzine pamoate (Vistaril):
- **f.** Naltrexone hydrochloride (Revia): $\binom{1}{1}$
- **g.** Other, (specify): $\begin{pmatrix} 1 \end{pmatrix}$

57. Has the patient taken any antihyperlipidemic medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	58.

(If yes, check all that apply):

- **a.** Atorvastatin (Lipitor):
- **b.** Colestipol hydrochloride (Colestid): (
- **c.** Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)
- **d.** Gemfibrozil (Gen-Fibro, Lopid):
- e. Fenofibrate (Tricor):
- **f.** Fluvastatin sodium (Lescol): (1)
- g. Lovastatin (Mevacor):
- **h.** Nicotinic acid (Niaspan): (1)
- i. Pravastatin sodium (Pravachol):
- j. Rosuvastatin (Crestor):
- **k.** Simvastatin (Zocor):
- **l.** Other, (specify):
- **58.** Has the patient taken any antiobesity medications in the past 3 months:



(If yes, check all that apply):

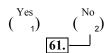
- a. Dexfenfluramine hydrochloride (Redux):
- **b.** Fenfluramine hydrochloride (Pondimin):
- c. Methamphetamine hydrochloride (Desoxyn, Gradumet): (1)
- **d.** Orlistat (Xenical):
- **e.** Phendimetrazine tartrate (Adipost, Bontril): (1)
- **f.** Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
- g. Sibutramine hydrochloride monohydrate (Meridia):
- **h.** Other, (specify):

59. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 3 months:

Yes	(No
1)	<u>0.</u>

(If yes, check all that apply):

- a. Acetaminophen (Tylenol):
- **b.** Aspirin 325 mg: (
- **c.** Aspirin 81 mg: (₁)
- **d.** Celecoxib (Celebrex):
- e. Ibuprofen (Advil, Motrin):
- **f.** Indomethacin (Indocin):
- g. Naproxen (Aleve, Naprosyn):
- **h.** Rofecoxib (Vioxx):
- **i.** Other, (specify):
- **j.** Other, (specify): (1)
- **60.** Has the patient taken any strong opiates containing acetaminophen medication in the past 3 months:



(If yes, check all that apply):

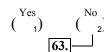
- **a.** Darvocet:
- **b.** Esgic Plus:
- c. Fioricet: (1)
- **d.** Lorcet: (1)
- e. Lortab:
- **f.** Norco:
- g. Percocet:
- **h.** Talacen:
- **i.** Tylenol #3: (₁)
- **j.** Tylenol #4: (₁)
- **k.** Tylox: (1)
- 1. Vicodin:
- **m.** Wygesic: (₁)
- **n.** Other, (specify): (

61. Has the patient taken any histamine H2 receptor antagonists/other gastrointestinal medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	62.

(If yes, check all that apply):

- **a.** Cimetidine (Tagamet):
- **b.** Esomeprazole magnesium (Nexium):
- **c.** Famotidine (Pepcid):
- **d.** Lansoprazole (Prevacid):
- e. Nizatidine (Axid):
- **f.** Omeprazole (Prilosec):
- g. Ranitidine (Zantac):
- **h.** Ranitidine bismuth citrate (Tritec):
- i. Antacids, (specify):
- **j.** Other, (specify):
- **62.** Has the patient taken any anticoagulant/antiplatelet medications in the past 3 months:



(If yes, check all that apply):

- **a.** Clopidogrel (Plavix):
- **b.** Dipyridamole: (₁)
- c. Heparin:
- **d.** Ticlopide (Ticlid):
- e. Warfarin (Coumadin):
- **f.** Other, (specify):

63. Has the patient taken any systemic corticosteroids in the past 3 months:

j. Other, (specify):

Yes	1	۷o (
(1)	(2)
[6	54. —	J
(If yes, check all that apply):		
a. Betamethasone sodium (Celestone):	(1)
b. Cortisol:	(1)
c. Cortisone:	(1)
d. Dexamethasone (Decadron):	(1)
e. Hydrocortisone (Hydrocortone):	(1)
f. Methylprednisolone (Solu-Medrol):	(1)
g. Prednisolone (Prelone):	(1)
h. Prednisone:	(1)
i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort):	((ر

64. Has the patient taken any cardiovascular/antihypertensive medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	65.

(If yes, check all that apply):

- **a.** Amiodarone (Pacerone):
- **b.** Amlodipine besylate (Norvasc):
- c. Atenolol (Tenormin):
- **d.** Benazepril (Lotensin):
- e. Captopril (Capoten):
- **f.** Clonidine (Catapres):
- g. Digoxin (Lanoxin):
- **h.** Diltiazem (Cardizem):
- i. Doxazosin (Cardura):
- j. Enalapril (Vasotec):
- **k.** Felodipine (Plendil):
- **I.** Furosemide (Lasix):
- **m.** Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)
- **n.** Hydrochlorothiazide + triamterene (Dyazide): (1)
- o. Lisinopril (Prinivil, Zestril):
- **p.** Losartan potassium (Cozaar): (1)
- **q.** Losartan potassium with hydrochlorothiazide (Hyzaar): (1)
- r. Metoprolol (Lopressor):
- s. Nifedipine (Adalat, Procardia):
- **t.** Perhexiline maleate: (1)
- **u.** Propranolol (Inderal):
- v. Quinapril (Accupril):
- w. Terazosin (Hytrin):
- **x.** Timolol maleate (Blocadren):
- y. Valsartan (Diovan):
- z. Verapamil (Calan):
- aa. Other, (specify):
- **ab.** Other, (specify):

1)

65. Has the patient taken any estrogen, progestin, hormone replacement therapy, or selective estrogen receptor modulators in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	66.

(If yes, check all that apply):

- a. Conjugated estrogen (Premarin/Prempro): (1)
- **b.** Diethylstilbestrol and methyltestosterone (Tylosterone):
- **c.** Esterified estrogen (Estratab, Menest): (1)
- **d.** Estradiol (Estrace): (1)
- **e.** Ethinyl estradiol (Estinyl): $\begin{pmatrix} 1 \end{pmatrix}$
- **f.** Fluoxymesterone (Android-F, Halotestin):
- **g.** Levonorgestrel (Norplant): (1)
- **h.** Medroxyprogesterone (Cycrin, Provera): (1)
- i. Megestrol (Megace):
- **j.** Methyltestosterone (Android): $\binom{1}{1}$
- **k.** Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): $\begin{pmatrix} & & & & \\ & & & & \end{pmatrix}$
- **l.** Norethindrone (Micronor):
- m. Norgestrel (Ovrette):
- **n.** Oral contraceptives: (1)
- o. Oxandrolone (Oxandrin):
- **q.** Progesterone (Prometrium): $\binom{1}{1}$
- r. Raloxifene (Evista): (1)
- s. Tamoxifen (Nolvadex):
- **t.** Other, (specify): (1)
- . Other, (*spectly)*.
- **u.** Other, (specify): $\begin{pmatrix} 1 \end{pmatrix}$

66. Has the patient taken any allergy or asthma medications in the past 3 months:

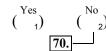
Yes	(No
(1)	(2)
	67.

(If yes, check all that apply):

- **a.** Beclomethasone dipropionate (Beclovent, Vanceril):
- **b.** Budesonide (Pulmicort, Rhinocort):
- **c.** Fluticasone propionate (Flonase, Flovent):
- **d.** Loratadine (Claritin):
- e. Mometasone furoate (Nasonex):
- **f.** Triamcinolone acetonide (Azmacort, Nasacort): $\begin{pmatrix} & & & \\ & & & \end{pmatrix}$
- **g.** Other, (specify):
- **h.** Other, (specify):
- **67.** Has the patient taken a multivitamin regularly in the past 3 months:

Yes	No
()	()
(1/	(2)

68. Has the patient taken vitamins other than multivitamins in the past 3 months:



- **69.** Which vitamins has the patient taken *(check all that apply)*:
 - a. Vitamin B (any type):
 - **b.** Vitamin C:
 - c. Vitamin D: (1
 d. Vitamin E: (1
 - e. Other, (specify):

70. Has the patient taken any supplements in the past 3 months:

	Yes	N	lo /
	(1)	71.	2 <i>)</i>]
(If yes, check all that apply):		/1.	
a. Alpha-lipoic acid:		(1)
b. Alpha-tocopherol:		(1)
c. Beta-carotene:		(1)
d. Betaine (Cystadane):		(1)
e. Calcium (any form):		(1)
f. Carnitine (any form):		(1)
g. Chondroitin (any form):		(1)
h. Choline + methionine + beta		,	,
adenosine + pyridoxine (Ep	ocler):	(1)
i. Cod liver oil:		(1)
j. Coenzyme Q:		(1)
k. Dichloroacetate:		(1)
I. Echinacea:		(1)
m. Fish oil (any form):		(1)
n. Flax seed oil:		(1)
o. Garlic:		(1)
p. Ginkgo biloba:		(1)
q. Glucosamine (any form):		(1)
r. Lecithin:		(1)
s. Magnesium:		(1)
t. Milk thistle:		(1)
u. N-acetyl-cysteine:		(1)
v. Potassium (any form):		(1)
w. S-adenylmethionine (SAM-	e):	(1)
x. Saw palmetto:		(1)
y. Selenium:		(1)
z. St. John's Wort:		(1)
aa. Taurine:		(1)
ab. Zinc picolinate:		(1)
ac. Other, (specify):		(1)

71. Has patient taken any of the following medications or other supplements/medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	72.

(If yes, record all other supplements/medications):

- **a.** Demeclocycline (Declomycin): (1)
- **b.** Divalproex (Depakote): (1)
- c. Doxycycline (Monodox):
- **d.** Isotretinoin (Accutane):
- e. Levothyroxine (Levoxyl, Synthroid):
- **f.** Liothyronine (Cytomel):
- **g.** Methotrexate (Rheumatrex):
- **h.** Minocycline (Dynacin, Minocin):
- i. Oxytetracycline (Terramycin):
- 1. Oxytetracycline (Terramychi).
- j. Penicillamine (Cuprimine, Depen):

 k. Tetracycline (Achromycin):
- I. Trientine hydrochloride (Syprine):
- The state of the s
- **m.** Ursodeoxycholic acid (Actigall, Urso, Ursodiol):
- **n.** Valproate sodium (Depacon):
- **o.** Valproic acid (Depakene):
- **p.** Other, (specify):
- **q.** Other, (specify):
- r. Other, (specify):

ad. Other, (specify):

1)

Patient		
1 aucit	 	

I	Adn	niniet	rativa	a info	rmation

day

72. Study Physician PIN:
73. Study Physician signature:
74. Clinical Coordinator PIN:
75. Clinical Coordinator signature:
76. Date form reviewed:
76. Date form reviewed.

mon

year

IR - Liver Imaging Studies Report

Purpose: To record liver imaging study results.

When: As needed during screening (visit t0) and follow-up (visits t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480).

Administered by: Clinical Coordinator.

Instructions: Complete this form at each of the visits listed above if the Baseline Medical History (BG) or Follow-up Medical History (HI) form says that a liver imaging study was obtained in the specified period. The form will allow you to skip out of sections that are irrelevant to your patient. What you will report at each visit are the results of the most recent scan of each type done in the 6 months prior to screening (visit t0) or in the period since the prior study visit (after enrollment). These will likely be standard of care scans with results obtained via medical records. In each case, answer the items based on review of the report; the Study Physician must review and approve the findings recorded on this form.

. Center, patient, and visit identification 10. Findings suggestive of NAFLD, NASH-related cirrhosis, or others of significance (check all that apply)			
	a. Fatty infiltration:	(12
2. Patient ID:	b. Cirrhosis:	(12
3. Patient code:	c. Hepatomegaly:	(12
	d. Hepatic mass:	(12
4. Date of visit:	e. Intrahepatic biliary dilatation:	(1/
	f. Extrahepatic biliary dilatation:	(1/
day mon year	g. Gallstones/cholelithiasis:	(12
5. Visit code:	h. Gall bladder polyps:	(12
	i. Cholecystectomy:	(12
6. Form & revision:i _ r1	j. Splenomegaly:	(12
7. Study: NAFLD Database 2 6	k. Ascites:	(12
	l. Other features of portal		•
B. Upper abdominal ultrasound	hypertension (specify):	(1
8. Did the patient have an upper abdominal ultrasound in the past 6 months (screening)/since the last visit (follow-up): Yes No 1 2	m. Other abnormality (specify):	(1.
9. Date of most recent upper abdominal ultrasound:	n. None of the above:	(12

C. Upper abdominal CT scan

11. Did the patient have an upper abdominal CT scan in the past 6 months (*screening*)/ since the last visit (*follow-up*):

(Y	es 1	(ار (د
	•	14.	_ ل

12. Date of most recent upper abdominal CT scan:

day	mon	year
gs suggestive (of NAFLD,	

13. Findings suggestive of NAFLD, NASH-related cirrhosis, or others of significance (check all that apply)

a. Fatty infiltration:	(1)
b. Cirrhosis:	(1)
c. Hepatomegaly:	(1)
d. Hepatic mass:	(1)
e. Hepatic hemangioma:	(1)
f. Hepatic cyst:	(1)
g. Intrahepatic biliary dilatation:	(1)
h. Extrahepatic biliary dilatation:	(1)
i. Gallstones/cholelithiasis:	(1)
j. Gall bladder polyps:	(1)
k. Cholecystectomy:	(1)
l. Splenomegaly:	(1)
m. Ascites:	(1)

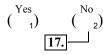
o. Other abnormality (specify): $\binom{1}{1}$

n. Other features of portal hypertension (*specify*):

n. None of the above:	(,

D. Upper abdominal MRI

14. Did the patient have an upper abdominal MRI in the past 6 months (*screening*)/ since the last visit (*follow-up*):



15. Date of most recent upper abdominal MRI:

		<u> </u>
day	mon	year

16. Findings suggestive of NAFLD, NASH-related cirrhosis, or others of significance *(check all that apply)*

f Hanatia areate

m. None of the above:

a. Fatty infiltration:	(1)
b. Cirrhosis:	(1)
c. Hepatomegaly:	(1)

d. Hepatic mass:	(1)
e. Hepatic hemangioma:	(1)

i. Hepatic cyst.	(1/
g. Intrahepatic biliary dilatation:	(1)

i. Spienomegary:	(1/
i Ascites:	()

k. Other features of portal		
hypertension (specify):	(1)

(1)

1)

1)

Dationt ID:			
Patient ID:	 $\overline{}$	$\overline{}$	

L.	Adn	ninisti	otivo	inforn	aatian
Н.,	Aan	ninisti	ative	intorn	iation

day

17.	Study Physician PIN:
18.	Study Physician signature:
19.	Clinical Coordinator PIN:
20.	Clinical Coordinator signature:
21.	Date form reviewed:

mon

year

NASH CRN NAFLD Database

CONFIDENTIAL: Not for Citation or Distribution

NAFLD Database Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
AN	Serious Adverse Event Report
ВС	Blood Collection for DNA
BD	Food Questionnaire Documentation
BG	Baseline History
BP	Blood Processing for Plasma and Serum
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
DR	Death Report
ED	Database Enrollment
FI	Family Member Identification
HE	Histology Findings for Most Recent Liver Biopsy Done Prior to Database Registration
HF	Liver Biopsy Histology Findings
HG	Histology Findings for Next Most Recent Liver Biopsy Done Prior to Database
	Registration
HI	Follow-up Medical History
ΙE	Interim Event Report
IR	Liver Imaging Studies Report
LD	Lifetime Drinking History (Skinner)
LP	Symptoms of Liver Disease (Children)
LQ	Symptoms of Liver Disease
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LT	Liver Tissue Banking
MA	Modifiable Activity Questionnaire
MV	Missed or Incomplete Visit
PA	Physical Activity
PE	Physical Examination
PF	Focused Physical Examination
PQ	Pediatric QOL: Parent Report for Teens (Age 13-17)

PR	Pediatric QOL: Parent Report for Children (Age 8-12)
PS	Pediatric QOL: Parent Report for Young Children (Age 5-7)
PT	Pediatric QOL: Parent Report for Toddlers (Age 2-4)
PV	Pediatric QOL: Young Child Report (Age 5-7)
PW	Pediatric QOL: Child Report (Age 8-12)
PY	Pediatric QOL: Teen Report (Age 13-17)
QF	MOS 36-Item Short-Form Health Survey
RC	Rescreen Form
RG	Registration
SD	Liver Biopsy Materials Documentation
SE	Most Recent Prior Liver Biopsy Materials Documentation
SF	Next Most Recent Prior Liver Biopsy Materials Documentation
TN	Transfer Notification

A

AD – Alcohol Use Disorders Identification Test (AUDIT)

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.

When: Visit s1.

Administered by: Self-administered (age 13 or older), interviewer administered (age 8-12). Clinical Coordinator must be available at visits to answer questions and review completed forms.

Respondent: Patient, age 8 or older. Patients age 13 or older should complete the form without help from spouse or family. Clinical Coordinator/parent can assist patients age 8-12.

Instructions: Flash Card #15, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator then should complete section B below.

. Ce	enter, patient, and vis	sit identification		dministrative information To be completed by Clinical Coordinator after
1.	Center ID:			urvey is completed.)
2.	Patient ID:		8.	How was the questionnaire completed:
3.	Patient code:			Self-administered by patient (1)
4.	Date of visit (date p	atient completed the form):		10. ◀
	day	mon year		Interview in English (2) Interview with translator (3)
5.	Visit code:	<u>s</u> <u>1</u>	9.	Who was the respondent (check all that apply):
6.	Form & revision:	<u>a</u> <u>d</u> <u>1</u>		 a. Patient: (1) b. Patient's mother or female guardian: (1)
7.	Study:	NAFLD Database 1		 c. Patient's father or male guardian: (1) d. Other (specify): (1)
				specify
			10.	Clinical Coordinator a. PIN: b. Signature:
			11.	Date form reviewed:
				day mon year

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below *(items 1-11 are for clinical center use only)*.

12. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times a month	Two to three times a week	Four or more times a week
(0	(1)	(2)	(3)	(4)
<u> </u>				

13. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more
(0	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

14. How often do you have six or more drinks on one occasion?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

15. How often during the last year have you found that you were not able to stop drinking once you had started?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

16. How often during the last year have you failed to do what was normally expected from you because of drinking?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$

Patient ID:		

17.	How often during the last year have you needed a first drink in the morning to get yourself going after
	a heavy drinking session?

	Less than			Daily or	
Never	monthly	Monthly	Weekly	almost daily	
(0	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(4)	

18. How often during the last year have you had a feeling of guilt or remorse after drinking?

Less than			Daily or	
Never	monthly	Monthly	Weekly	almost daily
(0)	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(4)

19. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 4 \end{pmatrix}$

20. Have you or someone else been injured as a result of your drinking?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

21. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

	Yes, but not in	Yes, during
No	the last year	the last yea
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

22. Today's date:

Thank you for completing this questionnaire.

AN - Serious Adverse Event Report

Purpose: To report occurrence of a serious, unexpected, adverse event reportable to the NAFLD Database (eg, events which are fatal or life threatening, result in significant or persistent disability, require or prolong hospitalization, result in a congenital anomaly or birth defect, or represent other significant hazard or serious harm to research subjects or others including breach of confidentiality, in the opinion of the investigators and are thought to be associated with NAFLD Database participation).

When: As needed, whenever a reportable serious adverse event is reported or a followup report is needed for a previously reported serious adverse event. When the event <u>does</u> <u>not</u> meet the reportable, serious adverse event criteria, use the IE form to report the event.

By whom: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form. The short name (item 23) and the severity code (item 24) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is avalailable at www.nashcrn.com. Click on Documents and then click on General Documents. Report the event to your IRB. Send the Data Coordinating Center the following: a copy of this form, a narrative description of the event, and a copy of your report to your IRB.

Followup report: A followup report should be filed (use this form) when the serious adverse event is resolved, or if there has been a significant change in the patient's condition or the physician's judgment about the event since the previous report was filed. The Study Physician should use his/her judgment in deciding what is significant.

NASH CRN Data Coordinating Center telephone number: (410) 955-8175

A. Center, patient and v 1. Center ID:	visit identificati	on	11. In the past, did the patient ever study drug for a main NASH treatment trial (eg, PIVENS, substudy (check all that apply)	CRN TONIC) or
2. Patient ID:			a. None:	(1.
3. Patient code:			b. Pioglitazone:	12.
			c. Vitamin E:	(1)
4. Date of report:			d. Metformin:	(1)
day	 mon	vear	e. Placebo:	(1)
,		year	f. Other (specify):	(1)
5. Visit code	_a NAFLD l	<i>fill in "n."</i>	specify 12. Is the patient currently receive drug or intervention for a NA pilot or feasibility study or an study:	ing a study SH CRN cillary
B. Participant informat	ion			$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
8. Date enrolled in NA	FLD Database:			14.
day		year	13. Specify the study drug or inte	ervention:
9. Gender:				
Male		$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
Female		$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$		
10. Age at time of event	::			
		Veare		

14. In the past, has the patient ever received a study drug or intervention for a NASH CRN pilot or feasibility study or ancillary study:

(Y	res 1	(No)
		16.	

15. Specify the study drug or intervention:

C. Serious adverse event description

16. Date of event onset:

-		_=
day	mon	year

17. Date event was reported to center:

day	mon	year

18. Describe the adverse event:

-		
-		

19. Medications in use at time of adverse event:

20.	Specify	tests/tr	reatmen	ts:		
	Specify	10010/11	caminon			

21. Did the event result in significant sequelae:

	$\binom{\mathrm{Yes}}{1}$	(No 2)
Specify:	2	2.
Speedy.		

22. Is this the first report or a followup report for this adverse event:

First report	(1)
Followup report	(2)

- **23.** Short name for adverse event (short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents):
- 24. Severity grade (3-5) (Severity grades are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents; use NAFLD Database forms HI, IE, and LR to report adverse events of Grade 1 (mild) or Grade 2 (moderate); do not key this form; call the DCC if unsure what to do.):

Grade 3 - Severe	$\begin{pmatrix} 1 \end{pmatrix}$
Grade 4 - Life threatening or disabling	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
Grade 5 - Death	(*,)

25. Did the event result in any of the following *(check all that apply)*

a.	Emergency department/urgent care	
	visit:	(

c. Significant or persistent disability:
$$\begin{pmatrix} 1 \end{pmatrix}$$

d. Congenital anomaly or birth defect:
$$\begin{pmatrix} 1 \end{pmatrix}$$

•	Otner	signiii	cant na	zaru or	narm	•	(1)

	specify		
None of the above		(1)

g.

1)

^{*}Complete and key Death Report (DR) form.

D. Association with NASH CRN

26. Is the adverse event due to a prior NASH CRN study drug or intervention from any source (PIVENS or TONIC trials, ancillary study, pilot or feasibility study):

Definitely yes	(1)
Probably yes	(2)
Possibly yes	(3)
Probably no	(4)
Definitely no	(5)

27. Current status of adverse event (check only one):

Resolved	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
Active	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
Unknown	29. (₃)
	29.

28. Date resolved:

day

29. Additional comments on adverse event:					

mon

year

E. Administrative information

- 30. Study Physician PIN:
- **31.** Study Physician signature:
- 32. Clinical Coordinator PIN:
- **33.** Clinical Coordinator signature:
- **34.** Date form reviewed:

_		_
day	mon	year

Key this form and send the DCC:

- (1) A copy of this form(2) A narrative description of the event(3) A copy of your report to your IRB.

BC - Blood Collection for DNA

Purpose: Document the collection of whole blood for shipment to NIDDK Genetics Repository at Rutgers University for DNA extraction. Complete this form only if the patient signed the consent for genetic research.

When: Visit s2 and as needed during followup (during followup, use the visit code of the followup visit that is open). **By whom**: Clinical Coordinator and laboratory personnel responsible for collection of whole blood.

Instructions: (1) Fill two 10 mL EDTA vacutainer tubes with whole blood. (2) Pack and ship the whole blood in the EDTA tubes to the NIDDK Genetics Repository at Rutgers University on the same day blood is collected. Ship at ambient room temperature. Ship whole blood in the specimen shippers supplied by the NIDDK Genetics Repository.

A. Center, patient and visit identification	10. Date and time of blood draw			
1. Center code:	a. Date:			
2. Patient ID:	day mon year			
3. Patient code:	b. Time:			
4. Date of visit:	hour iminute (1) (2			
day mon year	11. Number of 10 mL EDTA tubes:			
5. Visit code:	12. Form copy of tube labels:			
6. Form & revision: <u>b c 1</u>	NAFLD DB Form BC			
7. Study: NAFLD Database 1	Pt: ccc- 9999, xyz Gender			
B. Check on consent	Age, yrs.: XX			
8. Did the patient/parent consent/assent to blood draw for DNA extraction:				
$\binom{\operatorname{Yes}}{1}$ $\binom{\operatorname{No}}{*}_{2}$	13. Phlebotomist:			
* You cannot proceed until you get consent.	print name			
Tou cunnoi proceeu until you get consent.	D. Administrative information			
C. Specimen for Genetics Repository	14. Clinical Coordinator PIN:			
Attach ID labels to two 10mL EDTA tubes and fill each with whole blood; invert each tube gently 6 times to mix blood with additives; keep tubes at room temperature until the same day shipment to	15. Clinical Coordinator signature:			
the NIDDK Genetics Repository.9. Was blood collected for the NIDDK	16. Date form reviewed:			
Genetics Repository:	day mon year			
Yes (1)	, , 			
No, (specify):				

14.

specify

BD - Food Questionnaire Documentation

When: Visits s2, f048, f096, f144, and f192. Administered by: Clinical Coordinator.

Purpose: To document completion of the age appropriate food questionnaire.

Instructions: Complete this form for patients age 2 or older. This form documents completion of the age appropriate food questionnaire (patients age 18 or older complete the Block Food Questionnaire; patients age 2 to 17 complete the Brief Food Questionnaire).

A. Center, patient, and visit identification	11. Who was the respondent (check all that ap	pply))
1. Center ID:	a. Patient:	(1)
	b. Patient's mother or female guardian:	(1)
2. Patient ID:	c. Patient's father or male guardian:	(1)
3. Patient code:	d. Other (specify):	(1)
4. Date form completed:	specify		
day mon year	12. Form copy of label applied to food questionnaire:		
5. Visit code:	NAFLD DB Form BD Pt: 9999,xyz		
6. Form & revision:bd2	= !		
7. Study: NAFLD Database 1	<i>Date</i> :		
B. Administration of food questionnaire	_		
8. Date food questionnaire booklet was	C. Administrative information		
completed:	13. Clinical Coordinator PIN:		
day mon year NOTE: The visit s2 food questionnaire may no have been completed more than 8 weeks (56 days prior to registration for the Database.	14. Clinical Coordinator signature:		
9. Which food questionnaire was completed <i>(check only one):</i>	15. Date form reviewed:		
Block 98 (1	day mon	year	
Brief Food Questionnaire (2	,)		
10. How was the Brief Food Questionnaire completed:			
Self administered by patient/parent (1)		
	2)		
Interview with translator (3)		

BG - Baseline History

Purpose: To collect baseline history information about the patient.

When: Visit s1.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient or patient's parent.

Instructions: Collect information by interview or chart review. If c is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for the NAFLD Database. If is checked for an item, the patient is ineligible and cannot enroll in the NAFLD Database. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

Α.	Center.	visit.	and	natient	identification
7 B.	Cuitti	1 1010	ullu	patient	Identification

1. Center ID:		
---------------	--	--

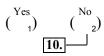
- **2.** Patient ID: ____ ___ ____
- 3. Patient code:
- **4.** Visit date (date this form is initiated):

day	mon	year

- **5.** Visit code: <u>s 1 ____</u> ___
- **6.** Form & revision: <u>b g 3</u>
- 7. Study: NAFLD Database 1

B. Family history

8. Do any of the patient's first degree relatives (parent, brother, sister, child) have liver disease:

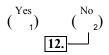


9. If yes, characterize the liver disease(s) *(check all that apply)*

a.	Alcohol	related	liver	disease:	(1)

specify

10. Do any of the patient's first degree relatives (parent, brother, sister, child) have cirrhosis:



11. If yes, is the cause of the cirrhosis unknown (cryptogenic):

$$(Yes)$$
 (No)

12. Do any of the patient's first degree relatives (parent, brother, sister, child) have diabetes (Type 1 or Type 2):

13.	Do any of the patient's first degree relatives (parent, brother, sister, child)			C. NAFLD history
	have obesity:			16. Date patient was fir
	Yes	(1)	fatty liver disease of cirrhosis:
	No	(2)	cirriosis.
	Don't know	(3)	day
14.	Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:	,		17. What prompted the NAFLD, NASH, or (check all that appl
	Yes	(1)	a. Symptoms for liv
	No Don't know	(2) 3)	b. Result of being e illness:
15.	Do any of the patient's first degree relatives (parent, brother, sister, child)			c. During a routine examination:
	have a problem with cholesterol or blood fat:			d. Blood donation:
	Yes	(1)	e. Other (specify):
	No	(2)	
	Don't know	(3)	
				18. What procedure/test diagnosis (check all

st diagnosed with r cryptogenic

day	mon	year

evaluation for cryptogenic cirrhosis

(eneen an mai appry)		
a. Symptoms for liver disease:	(1
b. Result of being evaluated for another illness:	(1
c. During a routine or insurance physical examination:	(1
d. Blood donation:	(1

specify

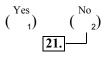
ts supported this first that apply)

a. Liver biopsy:	(1
b. Imaging studies (Ultrasound, CT, MRI):	(1
c. Elevated aminotransferases:	(1
d. Other (specify):	(1

Other (specify):	(1)	

specify

19. Does the patient have one or more liver biopsies done prior to registration in the Database that you want evaluated for the Database:



- **20.** Liver biopsy(s) prior to registration in the Database that you want evaluated
 - a. Date of most recent liver biopsy that you want evaluated for the Database (complete form SE [Most Recent Prior Liver Biopsy Materials Documentation] for this biopsy):

_		_
day	mon	year

b. Does the patient have another biopsy, older than the biopsy noted in item
20a, that you want evaluated for the Database:



c. Date of next most recent liver biopsy that you want evaluated for the Database (complete form SF [Next Most Recent Prior Liver Biopsy Materials Documentation] for this biopsy):

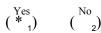
day	mon	year

21. Will the patient have a biopsy during screening:

$$\binom{\text{Yes}}{*}$$
 $\binom{\text{No}}{2}$

*Complete the Liver Biopsy Materials Documentation (SD) form for this biopsy.

22. Has the patient had a liver imaging study (ultrasound, MRI, or CT scan) in the past year:



*Complete the Liver Imaging Studies Report (IR) form.

D. Weight history

23. What was the patient's birthweight:

	_
lbs	oz

24. Review flashcard 17. Which (picture) best describes your weight pattern over the past 5 years (check only one):

Up and down, up and down	(1)
Up gradually	(2)
Up sharply (gained a lot in a brief interval))(3
Down gradually	(4)
Down sharply (lost a lot in a brief interval))(5)

25. What is the patient's current weight (ask the patient for his/her weight):

patient has ever	

lbs

lbs

27. At what age did the patient weigh the most:

	_	
age	in	years

28. Is the patient age 18 or older:

No or minimal change

26. What is the most the weighed:

29. What is the least the patient has ever weighed since age 18:

	lbs	
weigh the		

30. At what age did the patient weigh the least since age 18:

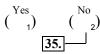
age in	years

31. Does the patient weigh more than he/she did one year ago:



32. How much more does the patient weigh now compared to one year ago:

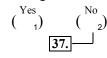
33. Does the patient weigh less than he/she did one year ago:



34. How much less does the patient weigh now compared to one year ago:

lbs	

35. Did the patient try to lose or gain weight:



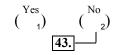
36. Which did the patient try to do *(check only one):*

Gain weight	(1)
Lose weight	(2)

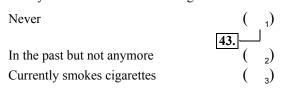
E. Tobacco cigarette smoking history

(interview with patient; not interview with parent, not by chart review)

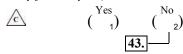
37. Is the patient age 8 or older:



38. Have you ever smoked tobacco cigarettes:



39. Did you smoke cigarettes regularly ("No" means less than 20 packs of cigarettes in a lifetime or less than 1 cigarette a day for one year):



40. How old were you when you first started regular cigarette smoking:



41. How old were you when you (last) stopped smoking cigarettes (code as "n" if you didn't stop smoking):

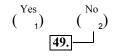
~		
	years	

42. On the average of the entire time you smoked cigarettes, how many cigarettes did you smoke per day:

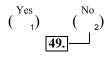
cigarettes/day

F. Menstrual history

43. Is the patient female:



44. Has menarche occurred:



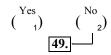
45. What was the patient's age at menarche:

age in years

46. Characterize the menstrual history in the past 5 years *(check only one):*

Regular periods	(12
Irregular periods	(2
Rare periods	(3
No periods	(`

47. Is patient post-menopausal:



48. What was the patient's age at menopause:

age in years

- **G. Medical history** (means Caution; condition is exclusionary if study physician agrees with diagnosis)
- **49.** Has the patient ever been diagnosed with and treated for any of the following *(check all that apply; source of information can be interview and/or chart review)*

a. Diabetes type 1:

7.1	`	17
b. Diabetes type 2:	(1)
c. Gestational diabetes (diabetes of pregnancy):	(1)
d. Hepatitis B:	(1)

1)

e. Hepatitis C:	A (1)	af. Hypertension: (1)
	<u></u>	ag. Cerebrovascular disease: (1)
f. Autoimmune hepatitis:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	ah. Dysbetalipoproteinemia:
g. Autoimmune cholestatic liver disc	order	<u></u>
(PBC or PSC):		ai. Hyperlipidemia (high cholesterol, high triglycerides): (1)
h. Wilson's disease:	(₁)	aj. Pancreatitis: (1)
	<u></u>	ak. Cholelithiasis: (1)
i. Alpha-1-antitrypsin (A1AT) defici	ency: (1)	al. Coronary artery disease: $\binom{1}{1}$
	<u></u>	am. Elevated uric acid such as gout: $\binom{1}{1}$
j. Iron overload:	(1)	an. Kidney disease: (1)
	<u>C</u>	ao. Polycystic ovary syndrome: (1)
k. Drug induced liver disease:	(1)	ap. Sleep apnea (not breathing
l. Gilbert's syndrome:	(1)	during sleep): $\begin{pmatrix} 1 \\ 1 \end{pmatrix}$ aq. Dermatologic disorders: $\begin{pmatrix} 1 \\ 1 \end{pmatrix}$
m. Esophageal or gastric varices on endoscopy:	(1)	ar. Myopathy:
n. Bleeding from varices:	$\begin{pmatrix} 1 \\ 1 \end{pmatrix}$	as. Myositis:
o. Other gastrointestinal bleeding:	$\begin{pmatrix} 1 \\ 1 \end{pmatrix}$	at. Major depression:
p. Ascites:	(₁)	au. Schizophrenia:
q. Edema:	(₁)	av. Bipolar disorder:
r. Hepatic encephalopathy:	(₁)	aw. Obsessive compulsive disorder:
s. Portal hypertension:	(₁)	ax. Severe anxiety or personality
t. Hepatorenal syndrome:	(,)	disorder: (1)
u. Hepatopulmonary syndrome:	$\begin{pmatrix} 1 \\ 1 \end{pmatrix}$	ay. None of the above: $\begin{pmatrix} 1 \end{pmatrix}$
v. Short bowel syndrome:	(1)	50. Has the patient ever had surgery for any
	$\langle c \rangle$	of the following (check all that apply)
w. Hemophilia (bleeding disorder):	(a. Stapling or banding of the stomach:
x. Systemic autoimmune disorder sur rheumatoid arthritis or systemic lu		b. Jejunoileal (or other intestinal) bypass:
y. Endocrine disease (hormonal abnormality):	(1)	c. Biliopancreatic diversion:
z. Hepatocellular carcinoma:	(₁)	
	<u>/c\</u> —	d. Other GI or bariatric surgery (specify): (1)
aa. Other malignancy (cancer):	(1)	
ab. Peripheral neuropathy:	(1)	e. None of the above:
ac. Seizure disorder or epilepsy:	(1)	
ad. Drug allergies:	(1)	

ae. Hypothyroidism:

 $\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$

51. Organ, limb, or bone marrow transplant		55.	Has the patient taken any alcohol abuse		
a. Has the patient ever received a liver transplant:			(dependance or withdrawal) medications in the past 6 months (check all that apply):		
Yes Yes	No		a. Chlordiazepoxide (Librium):	(1)
(₁)	§ (2)	b. Clorazepate dipotassium (Tranxene):	(1)
b. Has the patient ever received any	9		c. Diazepam (Valium):	(1)
other organ, limb, or bone marrow			d. Disulfiram (Antabuse):	(1)
transplant:	No		e. Hydroxyzine pamoate (Vistaril):	(1)
$\binom{\mathrm{Yes}}{1}$	(No	2)	f. Naltrexone hydrochloride (Revia):	(1)
52. Has the patient received total parenteral nutrition (TPN) in the past 2 years:			g. Other, (specify):	(1)
Yes (1)	(No	2)	h. None of the above:	(1)
53. Is the patient currently undergoing evaluation for bariatric surgery: (Yes	(No		Has the patient taken any antihyperlipidemic medications in the past 6 months (check all that apply):		
		2)	a. Atorvastatin (Lipitor):	(1)
H. Medication use			b. Colestipol hydrochloride (Colestid):	(1)
54. Has the patient used any antidiabetic medications in the past 6 months			c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate):	(1)
(check all that apply):	(`	d. Gemfibrozil (Gen-Fibro, Lopid):	(1)
a. Acarbose (Precose):		1)	e. Fenofibrate (Tricor):	(1)
b. Acetohexamide (Dymelor):		1)	f. Fluvastatin sodium (Lescol):	(1)
c. Chlorpropamide (Diabinese):		1)	g. Lovastatin (Mevacor):	(1)
d. Glimepiride (Amaryl):		1)	h. Nicotinic acid (Niaspan):	(1)
e. Glipizide (Glucotrol, Glucatrol XL):	(1)	i. Pravastatin sodium (Pravachol):	(1)
f. Glyburide (Micronase, DiaBeta, Glynase):	(1)	j. Rosuvastatin (Crestor):	(1)
g. Insulin:	,	1)	k. Simvastatin (Zocor):	(1)
h. Metformin (Glucophage, Glucophage XR):		1)	l. Other, (specify):	(1)
i. Miglitol (Glycet):		1)	m. None of the above:	(
j. Nateglinide (Starlix):		1)		•	17
k. Pioglitazone (Actos):		1)			
1. Repaglinide (Prandin):		1)			
m. Rosiglitazone (Avandia):		1)			
n. Tolazamide (Tolinase):		1)			
o. Tolbutamide (Orinase):		1)			
p. Other, (specify):		1)			

q. None of the above:

(1)

57.	Has the patient taken any antiobesity medications in the past 6 months (check all that apply):			59.	Has the patient taken any strong opiates containing acetaminophen medication in the past 6 months (check all that apply)		
	a. Dexfenfluramine hydrochloride				a. Darvocet:	(1)
	(Redux):	(1)		b. Esgic - Plus:	(1)
	b. Fenfluramine hydrochloride (Pondimin):	(1)		c. Fioricet:	(1)
	c. Methamphetamine hydrochloride	(17		d. Lorcet:	(1)
	(Desoxyn, Gradumet):	(1)		e. Lortab:	(1)
	d. Orlistat (Xenical):	(1)		f. Norco:	(1)
	e. Phendimetrazine tartrate (Adipost,	(`		g. Percocet:	(1)
	Bontril):	(1)		h. Talacen:	(1)
	f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):	(1)		i. Tylenol #3:	(1)
	g. Sibutramine hydrochloride		12		j. Tylenol #4:	(1)
	monohydrate (Meridia):	(1)		k. Tylox:	(1)
	h. Other, (specify):	(1)	1) 1) 1)	I. Vicodin:	(1)
					m. Wygesic:	(1)
	i. Other, (specify):	(1)		n. Other, (specify):	(1)
	j. None of the above:	(1)		o. None of the above:	(1)
58.	Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 6 months (check all that apply):			60.	Has the patient taken any histamine H2 receptor antagonists/other gastrointestinal medications in the past 6 months (check ali hat apply):	!	
	a. Acetaminophen (Tylenol):	(1)		a. Cimetidine (Tagamet):	(1)
	b. Aspirin - 325 mg:	(1)		b. Esomeprazole magnesium (Nexium):	(1)
	c. Aspirin - 81 mg:	(1)		c. Famotidine (Pepcid):	(1)
	d. Celecoxib (Celebrex):	(1)		d. Lansoprazole (Prevacid):	(1)
	e. Ibuprofen (Advil, Motrin):	(1)		e. Nizatidine (Axid):	(1)
	f. Indomethacin (Indocin):	(1)		f. Omeprazole (Prilosec):	(1)
	g. Naproxen (Aleve, Naprosyn):	(1)		g. Ranitidine (Zantae):	(1)
	h. Rofecoxib (Vioxx):	(1)		h. Ranitidine bismuth citrate (Tritec):	(1)
	i. Other, (specify):	(1)		i. Antacids, (specify):	(1)
	j. Other, (specify):	(1)		j. Other, (specify):	(1)
	k. Other, (specify):	<i>y</i>): (₁)		k. Other, (specify):	(1)	
	l. None of the above:	(1)		l. None of the above:	(1)

61.	Has the patient taken any anticoagulant/antiplatelet medications in the past 6 months (check all that apply):			63. Has the patient taken any cardiovascular or antihypertensive medications in the past 6 months (<i>check all that apply</i>):		
	a. Clopidogrel (Plavix):	(1)	a. Amiodarone (Pacerone):	(1)
	b. Dipyridamole:	(1)	b. Amlodipine besylate (Norvasc):	(1)
	c. Heparin:	(1)	c. Atenolol (Tenormin):	(1)
	d. Ticlopide (Ticlid):	(1)	d. Benazepril (Lotensin):	(1)
	e. Warfarin (Coumadin):	(1)	e. Captopril (Capoten):	(1)
	f. Other, (specify):	(1)	f. Clonidine (Catapres):	(1)
				g. Digoxin (Lanoxin):	(1)
	g. Other, (specify):	(1)	h. Diltiazem (Cardizem):	(1)
			12	i. Doxazosin (Cardura):	(1)
	h. None of the above:	(1)	j. Enalapril (Vasotec):	(1)
		(17	k. Felodipine (Plendil):	(1)
62.	Has the patient taken any systemic corticosteroids in the past 6 months			l. Furosemide (Lasix):	(1)
	(check all that apply): a. Betamethasone sodium (Celestone): b. Cortisol: c. Cortisone: d. Dexamethasone (Decadron):	(,	m. Hydrochlorothiazide (Esidrix, HydroDIURIL):	(1)
		(1)	n. Hydrochlorothiazide + triamterene		12
		(1)	(Dyazide):	(1)
		(1)	o. Lisinopril (Prinivil, Zestril):	(1)
		(1)	p. Losartan potassium (Cozaar):	(1)
	e. Hydrocortisone (Hydrocortone):	(1)	q. Losartan potassium with		
	f. Methylprednisolone (Solu-Medrol):	(1)	hydrochlorothiazide (Hyzaar):	(1)
	g. Prednisolone (Prelone):		1)	r. Metoprolol (Lopressor):	(1)
	h. Prednisone:	(1)	s. Nifedipine (Adalat, Procardia):	(1)
	i. Triamcinolone (Acetocot, Amcort,	(`	t. Perhexiline maleate:	(1)
	Aristocort, Kenacort):	(1)	u. Propranolol (Inderal):	(1)
	j. Other, (specify):	(1)	v. Quinapril (Accupril):	(1)
				w. Terazosin (Hytrin):	(1)
	k. Other, (specify):	(1)	x. Timolol maleate (Blocadren):	(1)
				y. Valsartan (Diovan):	(1)
	l. None of the above:	(1)	z. Verapamil (Calan):	(1)
				aa. Other, (specify):	(1)
				ab. Other, (specify):	(1)

ac. None of the above:

Has the patient taken any estrogen, progestin, hormone replacement therapy, or selective estrogen receptor modulators			65. Has the patient taken any allergy or asthma medications in the past 6 months (check all that apply):		
in the past 6 months (check all that apply):			a. Albuterol:	(1)
a. Conjugated estrogen (Premarin/Prempro):	(1)	b. Beclomethasone dipropionate (Beclovent, Vanceril):	(1)
b. Diethylstilbestrol and methyltestosterone (Tylosterone):	(1)	c. Budesonide (Pulmicort, Rhinocort):	(1)
c. Esterified estrogen (Estratab, Menest):	(1)	d. Fluticasone propionate (Flonase, Flovent):	(1)
d. Estradiol (Estrace):	(1)	e. Loratadine (Claritin):	(1)
e. Ethinyl estradiol (Estinyl):	(1)	f. Mometasone furoate (Nasonex):	(1)
f. Fluoxymesterone (Android-F, Halotestin):	(1)	g. Triamcinolone acetonide (Azmacort, Nasacort):	(1)
g. Levonorgestrel (Norplant):	(1)	h. Other, (specify):	(1)
h. Medroxyprogesterone (Cycrin, Provera):	(1)	——————————————————————————————————————		1/
i. Megestrol (Megace):	(1)	i. Other, (specify):	(1)
j. Methyltestosterone (Android):	(1)			
k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin):	(1)	j. None of the above:	(1)
l. Norethindrone (Micronor):	(1)	66. Has the patient taken a multivitamin regularly in the past 6 months:		
m. Norgestrel (Ovrette):	(1)	Yes (1)	1	No \
n. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon, Levlen, Levlite, Levora, Loestrin, Lo-Ovral, Necon, Nelova, Nordette, Norethin, Norinyl, Ortho Cyclen, Ortho-Novum, Ortho Tri-Cyclen, Ovral, Tri-Levlen, Triphasil, Trivora, Zovia):	(1)	67. Has the patient taken vitamins other than multivitamins in the past 6 months: (Yes (1)	((2) No 2)
o. Oxandrolone (Oxandrin):	(1)	68. Which vitamins has the patient taken <i>(check all that apply):</i>		
p. Oxymetholone (Anadrol):	(1)	a. Vitamin B (any type):	(1)
q. Progesterone (Prometrium):	(1)	b. Vitamin C:	(1)
r. Raloxifene (Evista):	(1)	c. Vitamin D:	(1)
s. Tamoxifen (Nolvadex):	(1)	d. Vitamin E:	(1)
t. Other, (specify):	(1)	e. Other, (specify):	(1)
u. Other, (specify):	(1)			
v. None of the above:	(1)			

9.	Has the patient taken any supplements in the past 6 months (check all that apply):			70. Has patient taken any of the following medications or other		
	a. Alpha-lipoic acid:	(1)	supplements/medications in the past 6 months (record all other		
	b. Alpha-tocopherol:	(1)	supplements/medications):		
	c. Beta-carotene:	(1)	a. Demeclocycline (Declomycin):	(1.
	d. Betaine (Cystadane):	(1)	b. Divalproex (Depakote):	(1.
	e. Calcium (any form):	(1)	c. Doxycycline (Monodox):	(1.
	f. Carnitine (any form):	(1)	d. Isotretinoin (Accutane):	(1.
	g. Chondroitin (any form):	(1)	e. Levothyroxine (Levoxyl, Synthroid):	(1.
	h. Choline + methionine + betaine +			f. Liothyronine (Cytomel):	(1.
	adenosine + pyridoxine (Epocler):	(1)	g. Methotrexate (Rheumatrex):	(1.
	i. Cod liver oil:	(1)	h. Minocycline (Dynacin, Minocin):	(1.
	j. Coenzyme Q:	(1)	i. Oxytetracycline (Terramycin):	(1.
	k. Dichloroacetate:	(1)	j. Penicillamine (Cuprimine, Depen):	(1.
	l. Echinacea:	(1)	k. Tetracycline (Achromycin):	(1.
	m. Fish oil (any form):	(1)	1. Trientine hydrochloride (Syprine):	(1.
	n. Flax seed oil:	(1)	m. Ursodeoxycholic acid (Actigall, Urso,		
	o. Garlie:	(1)	Ursodiol):	(1.
	p. Ginkgo biloba:	(1)	n. Valproate sodium (Depacon):	(1.
	q. Glucosamine (any form):	(1)	o. Valproic acid (Depakene):	(1.
	r. Lecithin:	(1)	p. Other, (specify):	(1.
	s. Magnesium:	(1)			
	t. Milk thistle:	(1)	q. Other, (specify):	(1
	u. N-acetyl-cysteine:	(1)			
	v. Potassium (any form):	(1)	r. Other, (specify):	(1.
	w. S-adenylmethionine (SAM-e):	(1)			
	x. Saw palmetto:	(1)	s. Other, (specify):	(1
	y. Selenium:	(1)	, , 1		1.
	z. St. John's Wort:	(1)	t. Other, (specify):		
	aa. Taurine:	(1)	~, (-F 27/).	(1.
	ab. Zinc picolinate:	(1)	u. None of the above:		
	ac. Other, (specify):	(1)	u. None of the above.	(1.
	ad. Other, (specify):	(1)			
	ae. None of the above:	(

I. Administrative information						
71. Study Physician PIN:	_					
72. Study Physician signature:						
73. Clinical Coordinator PIN:	_					
74. Clinical Coordinator signature:						
	_					
75. Date form reviewed:						

mon

year

day

year

NAFLD Database

BP - Blood Processing for Plasma and Serum

Purpose: Document collection of fasting blood for local separation of plasma and serum and shipment to NIDDK Biosample Repository at Fisher BioServices.

When: Visits s2, f048, f096, f144 and f192.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of whole blood. **Instructions**: Label CTAD and SST tubes of whole blood using labels specific for the patient and visit; these labels are generated by the clinic upon registration (screening labels) or after enrollment (followup visit labels). Attach duplicate whole blood tube labels in items 11 and 13. For plasma: Fill one 4.5 mL CTAD tube with whole blood. For serum: Fill four 10 mL SST red top tubes with whole blood. Process blood for plasma and serum within two hours. After separation, prepare 5 or 6 aliquots of plasma, depending on volume of plasma obtained: transfer 0.5 mL of plasma to each of 5 or 6 (2.0 mL) cryovials. After separation, prepare 40 aliquots of serum: transfer 0.5 mL of serum to each of 40 (2.0 mL) cryovials. Label aliquots with numbered patient-specific plasma (blue top) and serum (red top) cryovial labels provided by the DCC. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Affix serum aliquot #00 label and plasma aliquot #00 label to this form in item 18. The LS code (or Vcode if using old labels) keyed from the labels in item 18 of this form links the cryovials collected today with the date and visit identified in items 4 and 5 of this form. Freeze labeled aliquots of plasma and serum immediately according to procedures specified in the NAFLD Database SOP, Part I. NOTE: Immediately upon completion of plasma and serum aliquot preparation, destroy any leftover cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be able to be deter-

mincu.				
A. Center, patient and	visit identification	9. Date and tir	ne of blood d	raw
1. Center code:		a. Date:		
To Control Court.	<u> </u>		day	mon
2. Patient ID:		b. Time:	:	(
2. Detient en lee		hour	minute	- (
3. Patient code:		10. Number of	CTAD (blue-	top) tubes:
4. Date of visit:			`	17
day		11. Attach dupl	icate CTAD t	tube label:
5. Visit code:			B Form, BP P	21.
6. Form & revision:	<u>b</u> <u>p</u> <u>1</u>		9999, xyz vvvv	
7. Study:	NAFLD Database 1	Date:		_
n study.				
B. Processing whole blo Plasma and serum from whole blood Draw fasting blood	n aliquots are to be separated per instructions in the SOP.			
8. Was blood collecte Biosample Reposite				
Yes No, patient was not	t fasting for 12 hours $\begin{pmatrix} 1 \\ 2 \end{pmatrix}$			
No other reason (s	pecify): (23.			

specify other reason

Patient ID:		

12. Number of SST serum se (red-top) tubes:	parator tubes	18. Attach duplicate cryovial labels (use aliquot #00 labels which are located in the first row of labels in the set):
13. Attach duplicate SST seru tube labels:	um separator	Serum aliquot Plasma aliquot #00 label #00 label
NAFLD DB Serum 1	NAFLD DB Serum 2	
Pt: 9999, xyz	Pt: 9999, xyz	
Visit: vvvv	Visit: vvvv	
BP	BP	
Date:	Date:	
NAFLD DB Serum 3	NAFLD DB Serum 4	
Pt: 9999, xyz	Pt: 9999, xyz	19. Technician:
Visit: vvvv	Visit: vvvv	17. Technician.
BP	BP	print name
Date:	Date:	—
		D. Freezing aliquots
14. Phlebotomist:	t name	Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK BioSample Re-
prini	thanic	pository at Fisher BioServices.
C. Aliquots for plasma and s Pour 0.5 mL of plasma a mL pre-labeled cryovials serum into each of forty 2 cryovials.	into each of up to six 2.0 and pour 0.5 mL of	20. Date and time cryovials frozen in -70°C or -20°C a. Date: day mon year
15. Date and time of separation	on into plasma	b. Time:
and serum aliquots		hour minute am pm
a. Date:		nour minute um pin
	mon year	21. Number of cryovials frozen:
hour minute	$\binom{1}{am}$ $\binom{2}{pm}$	22. Technician:
16. Number of aliquots for pl	asma:	print name
17. Number of aliquots for serum:		E. Administrative information
		23. Clinical Coordinator PIN:
		24. Clinical Coordinator signature:
		25. Date form reviewed:
		day mon year

CG - Genetic Consent Documentation

Purpose: To document options selected for use of blood samples for genetic research.

When: Visit s2 and as needed during followup (during followup, use the visit code of the followup visit that is

By whom: Study Physician and Clinical Coordinator.

Instructions: Complete this form based on the consent documents signed by the patient/parent. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG

A. Center, patient and visit identification	11. Other information related to consent for genetic research that clinic staff feel		
1. Center ID:	needs to be keyed to the study database (e.g., if your genetic consent had other options that are not covered by the 3 categories of use of samples		
2. Patient ID:	specified above):		
3. Patient code:			
4. Date form completed:			
day mon year			
5. Visit code:			
6. Form & revision:cg1	12. In your judgment, has the patient/parent consented to collection of blood for DNA banking (this question is asked in recognition that not all IRBs will have approved consent statements		
7. Study: NAFLD Database 1B. Consent for collection, storage, and use of blood samples for current and future genetic research	that include language that can be mapped into the questions in items 8 through 10; a response of "No" to this question (item 12) means that blood should <u>NOT</u> be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):		
8. Does the patient/parent consent to genetic research on NAFLD or	$\begin{pmatrix} Yes \\ 1 \end{pmatrix} \qquad \begin{pmatrix} No \\ 2 \end{pmatrix}$		
cryptogenic cirrhosis that is currently planned by the study investigators:	C. Administrative information		
	13. Study Physician PIN:		
9. Does the patient/parent consent to future genetic research on NAFLD or	14. Study Physician signature:		
cryptogenic cirrhosis by this study or other study investigators: (Yes (No 1) (No 2)	15. Clinical Coordinator PIN:		
_	16. Clinical Coordinator signature:		
10. Does the patient/parent consent to future genetic research not related to NAFLD or cryptogenic cirrhosis by this study or			
other study investigators:	17. Date form reviewed:		
$\begin{pmatrix} \text{Yes} & \text{No} \\ \text{O} & \text{O} \end{pmatrix}$	day mon year		

year

NAFLD Database

CO - Database Closeout

Purpose: To temporarily close out NAFLD Database participation for a patient enrolled in the NAFLD Database in order for the patient to be randomized in another NASH CRN study. Once this form is keyed, the patient is exempt from completing visits in the NAFLD Database.

When: Ideally, upon randomization of the NAFLD Database patient into another NASH CRN study, but this form can be completed at any time. Use visit code n.

Administered by: Clinical coordinator.

Respondent: None.

Instructions: This form must be completed and keyed for patients enrolled in the NAFLD Database who are subsequently randomized in PIVENS, TONIC, or other NASH CRN study. Until it is keyed, the patient will remain on the active patient list, meaning that all Database visits are due for the patient. The keying of this form will turn off the visit windows for the NAFLD Database. If the patient is not randomized in the new study, this form should not be keyed. If it has already been keyed, it should be deleted.

A. Center, patient, and	l visit identificati	on	C. Administrative info	ormation
1. Center ID:		· —— ——	10. Clinical Coordinat	or PIN:
2. Patient ID:			11. Clinical Coordinat	or signature:
3. Patient code:			12. Date form reviewe	
4. Date of visit (date) for suspension of v	form in initiated; e isit completion):	effective date	day	mon
day	mon mon	year		
5. Visit code:	<u>n</u>			
6. Form & revision:	<u> </u>	_o_1_		
7. Study:	NAFLD Dat	tabase_1_		
3. New study informat	tion			
8. Study that patient h randomized in <i>(check only one)</i> :	as been or will be			
PIVENS		$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
TONIC		$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$		
Other (specify):		(3)		
	specify			
9. Date of randomizat (enter expected da randomized):	ion in new study ate if patient has	not yet been		
day		vear		

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee. By whom: Data Coordinating Center staff.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

	A. Clinic, patient and visit identification 1. Center ID
	2. Patient ID
	3. Patient code
///	4. Date of central reading
	5. Visit code
<u>c r 1</u>	6. Form and revision
	7. Study: 1 =Database; 2 =PIVENS; 3 =TONIC
///	8. Date of biopsy
	B. Slide sequence number9. Sequence number for a. H & E stained slide
	b. Masson's trichrome stained slide
	c. Iron stained slide
	d. Other slide
	Specify type of stain for other slide
	C. Administrative information 10. CC Initials
	11. CC Signature
///////	12. Date form reviewed
_	13. Tissue adequate: 0 =No → Request original slides from submitting clinic; 1 =Yes
	14. Followup with clinic (Specify):

Patient ID	D. Histology	
15. Biopsy length (mm)		
H & E stain		
	e.g., large and small droplet)	
a. Grade: 0 =<5%; 1 =5-33		
	central); 1=Zone 1 (periportal); 2=Azonal; 3=Panacinar	
c. Microvesicular steatos	sis, contiguous patches: 0 =Absent; 1 =Present	
17. Inflammation		
a. Amount of lobular infl	lammation: combines mononuclear, fat granulomas, and pmn foci:	
0 =0; 1 =<2 under 20x	x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag	
b. Microgranulomas seen		
c. Large lipogranulomas		
d. Amount of portal, chro	onic inflammation: 0 =None; 1 =Mild; 2 =More than mild	
18. Liver cell injury		
a. Ballooning: 0 =None; 1		
b. Acidophil bodies: 0 =R	· •	
	es (Kupffer cells): 0 =Rare/absent; 1 =Many	
d. Megamitochondria: 0 =	=Rare/absent; 1=Many	
19. Mallory's hyaline: 0 =Rar	re/absent; 1=Many	
20. Glycogen nuclei: 0 =Rare	/absent; 1=Many	
Masson's trichrome stain		
	1a=Mild, zone 3 perisinusoidal (requires trichrome);	
	erisinusoidal (does not require trichrome); 1c=Portal/periportal only;	
2 =Zone 3 and periportal,	any combination; 3 =Bridging; 4 =Cirrhosis	
22. Iron stain		
a. Hepatocellular iron gra	ade: 0=Absent or barely discernible, 40x → GOTO item 22c;	
1=Barely discernable	e granules, 20x; 2 =Discrete granules resolved, 10x; 3 =Discrete granules resolved,	4x;
4 =Masses visible by	·	
	stribution: 0 =Periportal; 1 =Periportal and midzonal; 2 =Panacinar; 3 =Zone 3 or azo	onal
	n grade: 0=None → GOTO item 23; 1=Mild; 2=More than mild	
	n distribution: 0 =Large vessel endothelium only; 1 =Portal/fibrosis bands only, but	more
than just in large ves	sel endothelium; 2 =Intraparenchymal only; 3 =Both portal and intraparenchymal	
23. Is this steatohepatitis? 0 =	No; 1a=Suspicious/borderline/indeterminate: Zone 3 pattern;	
1b=Suspicious/borderline	e/indeterminate: Zone 1, periportal pattern; 2 =Yes, definite	
24. Is cirrhosis present? 0 =No	to → GOTO item 27; 1=Yes	
 25. Is this cryptogenic cirrho	sis: 0=No → GOTO item 27; 1=Yes	
26. Features suggestive of ste	eatohepatitis etiology for cryptogenic cirrhosis:	
	e out cholate stasis): 0 =Absent; 1 =Present	
	away from septa: 0 =Absent; 1 =Present	
c. Hepatocyte ballooning	· · · · · · · · · · · · · · · · · · ·	
d. Megamitochondria: 0 =		
e. Other notable findings	: 0 =Absent; 1 =Present; Specify:	
27. Other comments:		

DR - Death Report

Purpose: To record the report of a patient's death.

When: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete this form whenever the clinical center is informed of a patient's death. If the death is considered associated or possibly associated with participation in the NAFLD Database, complete a Serious Adverse Event (AN) form and follow the directions on Form AN for reporting a SAE in the NAFLD Database.

A. Center, patient, and visit identification			10. Place of death:	
1. Center ID:			city/state/country	
2. Patient ID:			city/state/country	
3. Patient code:			11. Cause of death (Study Physician: use whatever knowledg have and your best medical judgment to best acterize the cause of death; check only one).	char-
	year		Heart disease	(1)
·	your		Stroke	(₂)
5. Visit code:n			Liver disease	(3)
		1	Malignancy	(4)
6. Form & revision: d	r	1	Other (specify):	(₅)
7. Study: NAFLD Datab	ase_	1	specify	
B. Death information			specify	
8. Date of death:			Unknown	(6)
day mon	year		C. Administrative information	
9. Source of death report (check all that ap	ply):		12. Study Physician PIN:	
a. Patient's family:	(1)		
b. Friend:	(1)	13. Study Physician signature:	
c. Health care provider or NASH CRN staff:	(1)	14. Clinical Coordinator PIN:	
d. Newspaper:	(1)	The Chimodi Coordinator Tity.	
e. Funeral parlor/home:	(1)	15. Clinical Coordinator signature:	
f. Medical record:	(1)		
g. Medical examiner:	(1)	16 Data farms mariamed	
h. Coroner:	(1)	16. Date form reviewed:	
i. Other (specify):	(1)	day mon ye	ar
other source				

other source

ED - Database Enrollment

Purpose: • Check eligibility for NAFLD Database.

• Record reasons for ineligibility for patients found to be ineligible.

When: Visit s2.

Administered by: Study Physician (adult hepatologist or pediatrician) and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: If is checked for any item, complete the entire form but note that the patient may not continue in the NAFLD Database. If an item has not been assessed because the patient is ineligible, write "m" (missing) next to that item. This form should be keyed for each patient for whom Form RG was completed without encountering a condition.

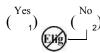
A. Center, patient, and	visit identification
1. Center ID:	
2. Patient ID:	
3. Patient code:	———
4. Visit date (date this)	form is initiated):
day	mon year
5. Visit code:	_s2
6. Form & revision:	_e_ d_ 2_
7. Study:	NAFLD Database 1

B. Alcohol use history consistent with NAFLD

8. On average, how many drinks containing alcohol has the patient had per week in the 2 years prior to screening:

Less than one drink a week	(1
One drink a week	(2)
2 to 4 drinks a week	(3)
5 to 7 drinks a week	(4)
8 to 10 drinks a week	(* 5)
11 to 14 drinks a week	(* 6)
15 or more drinks a week	$\left(\begin{array}{c} 1 \end{array}\right)$
	(Elig)—

9. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient's alcohol use since starting the screening process consistent with NAFLD:



C. Exclusions

- **10.** Do any of the patient's assessments show evidence of these medical exclusions
 - **a.** Total parenteral nutrition (TPN) within 3 months prior to screening:



b. Short bowel syndrome:



c. History of gastric or jejunoileal bypass prior to the diagnosis of NAFLD (bariatric surgery performed concomitant with or following the diagnosis of NAFLD is not exclusionary):



d. History of biliopancreatic diversion:



^{*} Patient is ineligible if female

- 11. Child-Pugh Turcotte score
 - **a.** Serum albumin subscore (from Form LR: > 3.5 g/dL = 1, 2.8-3.5 = 2, < 2.8=3):
 - **b.** Serum total bilirubin subscore (from Form LR: < 2.0 mg/dL=1, 2.0-3.0=2, > 3.0=3):
 - **c.** INR subscore (from Form LR: < 1.7=1, 1.7-2.3=2, > 2.3=3):
 - **d.** Ascites subscore (use all available information from all sources to score; None=1, Mild, easily managed=2, Severe, refractory=3):
 - e. Hepatic encephalopathy subscore (use all available information from all sources to score; None=1, Mild, easily managed=2, Severe, refractory=3):

 - **g.** Evidence of advanced liver disease (*Child-Pugh-Turcotte score at least 10*):

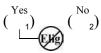


1-3

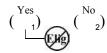
1-3

1-3

- **12.** Do any of the patient's assessments show evidence of these medical exclusions
 - **a.** Evidence of chronic hepatitis B as marked by the presence of HBsAg in serum (patients with isolated anti-HBc are not excluded):



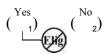
b. Evidence of chronic hepatitis C as marked by the presence of anti-HCV or HCV RNA in serum:



c. Low alpha-1-antitrypsin level and ZZ phenotype (*physician judgment*):



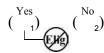
d. Wilson's disease:



e. Known glycogen storage disease:



f. Known dysbetalipoproteinemia:



g. Known phenotypic hemochromatosis (removal of > 4 g of iron by phlebotomy in an individual 18 or older):



h. Congenital hepatic fibrosis, polycystic liver disease:



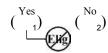
i. Other metabolic/congenital liver disease:



j. HIV infection or other systemic infectious disease:



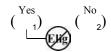
k. Disseminated or advanced extrahepatic malignancy:



I. Other severe systemic illness that in the opinion of the investigator would interfere with completion of followup:



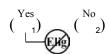
- **13.** Do any of the patient's assessments show evidence of these histologic exclusions
 - **a.** Hepatic iron index > 1.9:



b. Prominent bile duct injury (*florid duct lesions or periductal sclerosis*) or bile duct paucity:



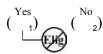
c. Chronic cholestasis:



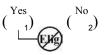
d. Vascular lesions (vasculitis, cardiac sclerosis, acute or chronic Budd-Chiari, hepatoportal sclerosis, peliosis):



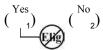
e. Iron overload greater than 3+:



f. Zones of confluent necrosis, infarction, massive or sub-massive, pan-acinar necrosis:



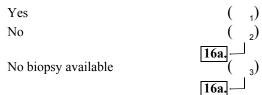
g. Multiple epithelioid granulomas:



14. Is there any other condition or issue that, in the opinion of the investigator, would interfere with the patient's adherence to study requirements:



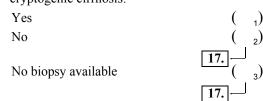
- D. Check on imaging and histologic criteria for inclusion in Database
- 15. 5% steatosis on biopsy
 - **a.** Did at least one biopsy show at least 5% steatosis:



b. Date of most recent biopsy showing at least 5% steatosis:

=	=	<u>=</u> -
day	mon	year

- **16.** Cryptogenic cirrhosis on biopsy
 - a. Did at least one biopsy show cryptogenic cirrhosis:



b. Date of most recent biopsy showing cryptogenic cirrhosis:

day	mon	year

17. Does the patient have an imaging study obtained in the past year that is suggestive of NAFLD (physician judgment, criteria not specified):

Yes		N	0
$\begin{pmatrix} 1 \end{pmatrix}$		(2)
Γ	19.	الـا	_

- **18.** Imaging studies suggestive of NAFLD *(check all that apply)*
 - **a.** Upper abdominal ultrasound: (1)
 - **b.** Upper abdominal CT scan: (1)
 - **c.** Upper abdominal MRI:
- **19.** Does the patient have an imaging study obtained in the past year compatible with cirrhosis (*small liver, nodularity, heterogeneous echo pattern*):

(Y	es 1)		(N	lo 2
•	[22.	<u> </u>	_

- **20.** Imaging studies suggestive of cirrhosis *(check all that apply)*
 - **a.** Upper abdominal ultrasound:
 - **b.** Upper abdominal CT scan: (1)
 - **c.** Upper abdominal MRI: (1)
- **21.** Does the patient have any of the following findings
 - a. Imaging evidence of portal hypertension (splenomegaly, portosystemic collaterals):

 ()
 - **b.** Albumin less than 3.5 g/dL: (1)
 - **c.** INR greater than 1.3:
 - **d.** Platelet count less than 140,000 cells/uL:
 - e. Esophageal or gastric varices on endoscopy: (1)
 - **f.** Ascites on physical exam or imaging study:
 - **g.** None of the above:

E. Diagnostic category for inclusion

22. Diagnostic category for inclusion *(check only one):*

Definite NAFLD on most recent biopsy (item 15a = Yes and date in item 15b is most recent biopsy date) (

most recent biopsy date) (1)
Definite NAFLD on biopsy in the past

but not on a subsequent biopsy (item 15a = Yes and date in item 15b is not the most recent biopsy date) ($_2$)

Definite cryptogenic cirrhosis on most recent biopsy (item 16a = Yes and date in item 16b is most recent biopsy date) (3)

Suspected NAFLD (item 17 = Yes and at least one of items 18a-c is checked) ($_4$)

Suspected (clinical) cryptogenic cirrhosis (item 19 = Yes and at least one of items 20a-c is checked and at least one of items 21a-f is checked)

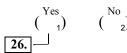
None of the above



year

F. Eligibility check

23. Was an ineligibility condition checked or an eligibility not ascertained in items 8-14 or item 22:



Instructions: Key visits s1 and s2 forms: RG and AD, BC, BD, BG, BP, CG, HF, IR, LD, LP/LQ, LR, LS, PA/MA, PE, PF, QF/PQ, PR, PS, PT, PV, PW, PY as appropriate. Run the Enrollment Task on your clinic data system.

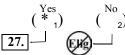
24. Were any STOP's or ineligible conditions other than "missing Form ED" identified by the Enrollment Task:

Yes	(
No	26. (2)
Tools not man become noticed in language		

Task not run because patient is known to be ineligible



- *You can skip running the Enrollment Task if you already know that the patient is ineligible; you must run the task to enroll the patient.
- 25. Does the patient/parent still consent/assent to enrollment (you should ask the patient/parent to orally affirm his/her consent/assent):



*Go to item 27 and complete this form. Then key this form and run the Enrollment Task on your clinic data system to enroll the patient.

G. Reasons for ineligibility for ineligible patients

NOTE: Complete this section for ineligible patients only.

26. Reason for ineligibility (check all that apply)

a.	Reason c	covered in	items	8-14, 2	22,		
	or 25:					(1)

- **b.** Tests are outside time window and clinic chose not to repeat tests:
- **c.** Other reason not covered on this form (specify):

H. Administrative information

27. Study Physician PIN:

40.	Study	Physiciai	i signature		

- **29.** Clinical Coordinator PIN: ____ ___
- **30.** Clinical Coordinator signature:
- **31.** Date form reviewed:

mon

FI - Family Member Identification

Purpose: To identify a NAFLD Database patient who has one or more close relatives, i.e., child (biological or not biological), siblings (full, half, or not biological) or parents (biological or not biological) enrolled in NAFLD Database, PIVENS or TONIC.

When: As needed. Complete one FI form for each NAFLD Database patient with children, siblings, or parents enrolled in NAFLD Database, PIVENS, or TONIC. Update form as needed during follow-up if additional children, siblings, or parents enroll in NAFLD Database, PIVENS, or TONIC.

By whom: Clinical coordinator.

Instructions: Form is to be completed if there is a patient enrolled in NAFLD Database who has one or more children, siblings, or a parent enrolled in NAFLD Database, PIVENS, or TONIC. The index patient's study identifiers are recorded in section A. Up to 5 children can be entered on a form in section B and up to 5 siblings can be entered on a form in section C. One mother and one father can be entered in section D. If there are more than 5 children, 5 siblings (not including the index patient), or 1 of each parent in NAFLD Database, PIVENS, and TONIC, call the DCC for directions.

Please note: Full and half siblings and biological children or parents do not need to live with the index patient. The not biological category would include non-blood related children, siblings, or parents spending most of their time in the same household as the index patient, i.e., adoptive, step, foster, etc. Call the DCC with any questions.

A. Center, visit, and patient identification	9. First child
1. Center ID:	a. Patient ID:
2. Patient ID:	b. Patient code:
3. Patient code:	c. Biological relationship to index patient <i>(select one):</i>
4. Date of visit:	Full (1) Not biological (2)
	Skip to item 14 if there are no more children enrolled in NAFLD, PIVENS, or TONIC.
6. Form & revision: <u>f i 1</u>	10. Second childa. Patient ID:
7. Study: NAFLD Database 1	b. Patient code:
B. Study identifiers of children of the index patient recorded in Section A	c. Biological relationship to index patient <i>(select one):</i>
8. How many children of the index patient identified in item 2 are enrolled in NAFLD Database, PIVENS, and TONIC	Full (1) Not biological (2)
(if no children, code ''0'' and skip to item 14; call the DCC if more than 5 children are enrolled in NAFLD Database, PIVENS, and TONIC):	Skip to item 14 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.
If zero (0), then skip to item 14.	

11. Third child	C. Study identifiers of sibling(s) of the index patient recorded in Section A
a. Patient ID:	•
b. Patient code:	14. How many siblings of the index patient identified in item 2 are enrolled in NAFLD Database, PIVENS, and TONIC
c. Biological relationship to index patient <i>(select one):</i>	(if no siblings, code ''0'' and skip to item 20; call the DCC if more than 5 siblings are enrolled in NAFLD Database, PIVENS, and TONIC):
Full (1)	0-5
Not biological (₂)	
	If zero (0), then skip to item 20.
Skip to item 14 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.	15. First sibling
12. Fourth child	a. Patient ID:
a. Patient ID:	b. Patient code:
b. Patient code:	c. Biological relationship to index patient (select one):
c. Biological relationship to index patient	Full (1)
(select one):	Half $\begin{pmatrix} 1 & 1 & 1 \\ 1 & 2 & 1 \end{pmatrix}$
Full (1)	Not biological (3)
Not biological (2)	
Skip to item 14 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.	Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.
1011201	16. Second sibling
13. Fifth child	a. Patient ID:
a. Patient ID:	
	b. Patient code:
b. Patient code:	
	c. Biological relationship to index patient
c. Biological relationship to index patient	(select one):
(select one):	Full (1)
Full (1)	Half (₂)
Not biological (2)	Not biological (3)
Call the DCC for instructions if there are more children enrolled in NAFLD Database, PIVENS, or TONIC.	Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

17.	Third sibling	D. Study identifiers of the parents of the index patient identified in section A (call the DCC if
	a. Patient ID:	more than 1 mother and/or 1 father are enrolled in NAFLD Database and PIVENS)
	b. Patient code:	20. Mother of index patient
	c. Biological relationship to index patient <i>(select one):</i>	 a. Is the mother of the index patient enrolled in NAFLD Database or PIVENS):
	Full (1)	
	Half (2)	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
	Not biological (3)	21.
	Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.	b. Patient ID:
	TOTALE.	c. Patient code:
18.	Fourth sibling	d Dialogical relationship to index nations
	a. Patient ID:	d. Biological relationship to index patient (select one):
		Full (1)
	b. Patient code:	Not biological (2)
	c. Biological relationship to index patient	21. Father of index patient
	(select one):	a. Is the father of the index patient
	Full (1)	enrolled in NAFLD Database or
	Half (2)	PIVENS):
	Not biological (3)	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
	Skip to item 20 if there are no more children	22.
	enrolled in NAFLD Database, PIVENS, or TONIC.	
		b. Patient ID:
19.	Fifth sibling	c. Patient code:
	a. Patient ID:	d. Biological relationship to index patient
	b. Patient code:	(select one):
		Full (1)
	c. Biological relationship to index patient <i>(select one)</i> :	Not biological (₂)
	Full (1)	E. Administrative information
	Half (2)	22. Clinical coordinator PIN:
	Not biological (3)	
	3)	23. Clinical coordinator signature:
	Call the DCC for instructions if there are more children enrolled in NAFLD Database, PIVENS, or TONIC.	
		24. Date form reviewed:
		day mon year

HE - Histology Findings for Most Recent Liver Biopsy Done Prior to Database Registration

Purpose: Record results of histologic evaluation of slides from **most recent liver biopsy done prior to Database registration.**

When: Visit s1.

By whom: Study Pathologist at the NASH CRN clinical center (this is not the form used for central reading) and Clinical Coordinator.

Instructions: The Study Pathologist should complete this form using the institution's H & E slide and if available, the institution's Masson's trichrome slide. Upon completion of this form, the Study Pathologist should give the original HF form to the Clinical Coordinator. If fewer than 2 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 2 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the Data Coordinating Center.

A. Center, patient and visit identification			C. NAFLD evaluation (use H & E and Masson's trichrome slides only)			
1. Center ID:				Ç,		
2. Patient ID:				10. Steatosis (assume macro, e.g., large an droplet)	d sn	nall
2. I wient ib.				a. Grade:		
3. Patient code:				< 5%	((0
3. I attent code.				5-33%	(1)
4. Date of reading:				34-66%	(2)
4. Date of reading.		_		> 66%	(3)
day	mon	year		b. Location:		-
	4			Zone 3	((0
5. Visit code:	_S1_			Zone 1	(1)
				Azonal	(2)
6. Form & revision:	_h	e	1	Panacinar	(3)
7. Study:	NAFLD D	atabase_	1	11. Fibrosis stage (Masson's trichrome stain)		
				0: None	((0
B. Biopsy information				1a: Zone 3, perisinusoidal (requires trichome)	(1)
8. Date this biopsy was <i>surgical pathology r</i> .		btained fi	rom	1b: Zone 3, perisinusoidal (easily seen on H&E)	(2)
=				1c: Portal/periportal only	(3)
day	mon	year		2: Zone 3 and periportal, any combination	(4)
9. What slides are to be				3: Bridging	Ì	5)
evaluation (check all	that apply)			4: Cirrhosis	Ì	6)
a. H & E:		(1)		`	0,
b. Masson's trichron	ne:	(,)			

12. Inflammation			18. Features of other forms of chronic liver		
a. Amount of lobular inflammation:			disease (check all that apply)	(`
combines mononuclear, fat granulomas, and pmn foci:			a. Vascular lesions of ALD/B-C/OVD:	(1)
0	(0	b. Inflammation suggestive of AIH, HCV:	(1)
< 2 / 20x mag	(1)	c. Pigment suggestive of HH:	(1)
2-4 / 20x mag	(2)	d. Globules suggestive of A1AT:	(1)
> 4 / 20x mag	(3)	e. Hepatocellular changes suggestive of	(1)
b. Amount of portal, chronic inflammation:			HBV:	(1)
None to minimal	(0)	f. Granulomas suggestive of sarcoid,	(`
Greater than minimal	(1)	PBC, infection:	(1)
13. Hepatocellular ballooning:			g. Other (specify):	(1)
None	(0)	h. None:	(
Few	(1)	II. None.	(1)
Many	(2)	E. Evaluation of cryptogenic cirrhosis		
14. Is steatohepatitis present:			19. Is cirrhosis present:		
No	(1)	Yes	N	lo (
Suspicious/borderline/indeterminate Yes, definite	(2)	(1)	_ (₂)
i es, definite	(3)	22	. —	
D. Exclusion of other liver disease			20. In your opinion, is this cryptogenic		
15. Is there evidence of primary biliary			cirrhosis (cirrhosis that fails to meet criteria for	NAF	LD
			and without anidones of other form (a) of		
cirrhosis:			and without evidence of other form(s) of liver disease):	chro	піс
	(1	oV 2)	liver disease): Yes	chro N	onic No
cirrhosis: (Yes 1)	(No 2)	liver disease): (Yes (1)	(^N	onic No 2
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease:	(2)	liver disease): (Yes (1)	(^N	onic No 2)
cirrhosis: (Yes 1)	(No 2)	liver disease): (Yes (1)	(^N	onic No 2)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (** 1) L (** 1)	()	2)	liver disease): (Yes 1)	(^N	onic No 2)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease:	()	2)	liver disease): (Yes (1) 22 F. Other features	(^N	No 2)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (** 1) L (** 1)	()	2)	liver disease): (Yes 1) 22 F. Other features 21. Other features (check all that apply)	(^N	√o 2)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (*1) * Caution: Wilson's disease is exclusio 17. Features of chronic cholestatic liver	()	2)	liver disease): (Yes 1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from	(^N	No 2)
* Caution: Wilson's disease is exclusion. * Caution: Wilson's disease is exclusion. * Caution: Wilson's disease is exclusion.	()	2) No 2)	liver disease): (Yes (1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa:	(^N	No 2) 1
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (*1) * Caution: Wilson's disease is exclusio 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis:	()	2) No 2)	liver disease): (Yes 1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning:	(^N	1)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (** 1) * Caution: Wilson's disease is exclusio 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis: b. Florid duct lesions:	()	2) No 2) 1) 1)	liver disease): (Yes 1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning: d. Megamitochondria:	(^N	1) 1) 1) 1)
* Caution: Wilson's disease is exclusio * Caution: Wilson's disease is exclusio 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis: b. Florid duct lesions: c. Cholate stasis:	()	2) No 2) 1) 1) 1)	liver disease): (Yes 1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning: d. Megamitochondria:	(^N	1) 1) 1) 1)
* Caution: Wilson's disease is exclusion * Caution: Wilson's disease is exclusion * Caution: Wilson's disease is exclusion 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis: b. Florid duct lesions: c. Cholate stasis: d. Copper deposition:	()	2) No 2) 1) 1) 1) 1)	Iiver disease): (Yes 1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning: d. Megamitochondria: e. Other (specify):	(^N	1) 1) 1) 1)

Patient ID:		

G. Other comments

22. Other comments:

H. Administrative information

27. Date form reviewed:

23. Study Pathologist PIN: ____ ___

24. Study Pathologist signature:

25. Clinical Coordinator PIN: ____ ___

26. Clinical Coordinator signature:

day mon year

HF - Liver Biopsy Histology Findings

Purpose: Record results of histologic evaluation of slides from liver biopsy done after registration in Database and before enrollment in Database.

When: Baseline visit s1 if biopsy slides are available and adequate for scoring.

By whom: Study Pathologist at the NASH CRN clinical center (this is not the form used for central reading) and Clinical Coordinator.

Instructions: The Study Pathologist should complete this form using the institution's H & E slide and if available, the institution's Masson's trichrome slide. Upon completion of this form, the Study Pathologist should give the original HF form to the Clinical Coordinator. If fewer than 2 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 2 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the Data Coordinating Center.

A. Center, patient and visit identification	C. NAFLD evaluation (use H & E and				
	Masson's trichrome slides only)				
1. Center ID:	_				
2. Patient ID:	10. Steatosis (assume macro, e.g., large and small droplet)				
	a. Grade:				
3. Patient code:	< 5%				
	5-33%				
4. Date of reading:	34-66%				
4. Date of feating.	> 66%				
day mon year	b. Location:				
	Zone 3 $\begin{pmatrix} 0 \end{pmatrix}$				
5. Visit code:s1	$-$ Zone 1 $\begin{pmatrix} \ddots & \ddots $				
	Azonal (2)				
6. Form & revision: _h_f1	Panacinar (3)				
7. Study: NAFLD Database 1	11. Fibrosis stage (Masson's trichrome stain)				
	0: None (₀)				
B. Biopsy information	1a: Zone 3, perisinusoidal (requires trichome) (1)				
8. Date this biopsy was performed <i>(obtained fro surgical pathology report):</i>	1b: Zone 3, perisinusoidal (easily seen on H&E)				
	1c: Portal/periportal only (3)				
day mon year	2: Zone 3 and periportal, any combination (4)				
9. What slides are to be used in this	3: Bridging (5)				
evaluation (check all that apply)	4: Cirrhosis (6)				
a. H & E: (1)				
b. Masson's trichrome: (1)				

12. I	nflammation			18. Features of other forms of chronic liver		
:	A. Amount of lobular inflammation:			disease <i>(check all that apply)</i> a. Vascular lesions of ALD/B-C/OVD:	(`
	combines mononuclear, fat granulomas, and pmn foci:				(1)
	0	(0	b. Inflammation suggestive of AIH, HCV:	(1)
	< 2 / 20x mag	(1)	c. Pigment suggestive of HH:	(1)
	2-4 / 20x mag	(2)		(
	> 4 / 20x mag	(3)	d. Globules suggestive of A1AT:	(1)
j	Amount of portal, chronic inflammation:			e. Hepatocellular changes suggestive of HBV:	(1)
	None to minimal	(0)	f. Granulomas suggestive of sarcoid,		
	Greater than minimal	(1)	PBC, infection:	(1)
13. I	Hepatocellular ballooning:			g. Other (specify):	(1)
	None	((0			
	Few	(1)	h. None:	(1)
	Many	(2)	E. Evaluation of cryptogenic cirrhosis		
14. I	s steatohepatitis present:			19. Is cirrhosis present:		
	No	(1)	Yes	N	No .
	Suspicious/borderline/indeterminate	(2)	(1)	(2)
	Yes, definite	(3)	22	. —	
D. Ex	clusion of other liver disease			20. In your opinion, is this cryptogenic		
	s there evidence of primary biliary cirrhosis: (Yes (1)	(1	No 2)	cirrhosis (cirrhosis that fails to meet criteria for and without evidence of other form(s) of liver disease): Yes (1)		
16. I	s there evidence of Wilson's disease:			22	.—	J
	(* 1)	(No 2)	F. Other features		
	* Ction. Wiles. 'a diaman is malusian			21. Other features <i>(check all that apply)</i>		
	* Caution: Wilson's disease is exclusion	ary		a. Mallory's hyaline (r/o cholate stasis):	(1)
	Features of chronic cholestatic liver lisease (check all that apply)			b. Perisinusoidal fibrosis away from septa:	(1)
	a. Bile duct loss/infiltration/sclerosis:	(1)	c. Hepatocyte ballooning:	(1)
I	b. Florid duct lesions:	(1)	d. Megamitochondria:	(1)
	c. Cholate stasis:	(1)	e. Other (specify):	(1)
(d. Copper deposition:	(1)			
	e. Other (specify):	(1)	f. None:	(1)
	\ 1 JJ/	(17			

G. Other comments

mon

year

HG - Histology Findings for Next Most Recent Liver Biopsy Done Prior to Database Registration

Purpose: Record results of histologic evaluation of slides from <u>next most recent</u> liver biopsy done prior to Database registration.

When: Visit s1.

By whom: Study Pathologist at the NASH CRN clinical center (this is not the form used for central reading) and Clinical Coordinator.

Instructions: The Study Pathologist should complete this form using the institution's H & E slide and if available, the institution's Masson's trichrome slide. Upon completion of this form, the Study Pathologist should give the original HF form to the Clinical Coordinator. If fewer than 2 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 2 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the Data Coordinating Center.

A. Center, patient and visit identification			C. NAFLD evaluation (use H & E and Masson's trichrome slides only)			
1. Center ID:			Masson's tremone shies only)			
2. Patient ID:			10. Steatosis (assume macro, e.g., large a droplet)	ind sr	nall	
2. Tuttont 15.			a. Grade:			
3. Patient code:			< 5%	(0	
3. I attent code.			5-33%	(1)	
4. Date of reading:			34-66%	(2)	
4. Date of feating.		_	> 66%	(3)	
day	mon	year	b. Location:			
	1		Zone 3	(0	
5. Visit code:	_S1_		Zone 1	(1)	
	1	1	Azonal	(2)	
6. Form & revision:	_h_	_ <u>_g</u>	Panacinar	(3)	
7. Study:	NAFLD Da	atabase 1	11. Fibrosis stage (Masson's trichrome stain	1)		
			0: None	(0	
B. Biopsy information			1a: Zone 3, perisinusoidal (requires trichome)	(1)	
8. Date this biopsy was surgical pathology re		tained from	1b: Zone 3, perisinusoidal (easily seen on H&E)	(2)	
 -		_=	1c: Portal/periportal only	(3)	
day	mon	year	2: Zone 3 and periportal, any combination	(4)	
9. What slides are to be			3: Bridging	(5)	
evaluation (check all	іпаі арріу)		4: Cirrhosis	(6)	
a. H & E:		(1)			-	
b. Masson's trichrom	e:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$				

12. Inflammation			18. Features of other forms of chronic liver		
a. Amount of lobular inflammation:			disease (check all that apply)	(`
combines mononuclear, fat granulomas, and pmn foci:			a. Vascular lesions of ALD/B-C/OVD:	(1)
0	(0	b. Inflammation suggestive of AIH, HCV:	(1)
< 2 / 20x mag	(1)	c. Pigment suggestive of HH:	(1)
2-4 / 20x mag	(2)	d. Globules suggestive of A1AT:	(1)
> 4 / 20x mag b. Amount of portal, chronic	(3)	e. Hepatocellular changes suggestive of	(17
inflammation:			HBV:	(1)
None to minimal	(0	f. Granulomas suggestive of sarcoid,	,	
Greater than minimal	(1)	PBC, infection:	(1)
13. Hepatocellular ballooning:			g. Other (specify):	(1)
None	(0			
Few	(1)	h. None:	(1)
Many	(2)	E. Evaluation of cryptogenic cirrhosis		
14. Is steatohepatitis present:			19. Is cirrhosis present:		
No	(1)	Yes	N	No (
Suspicious/borderline/indeterminate	(2)	(1)	_ (₂)
Yes, definite	(3)	22	. —	
D. Exclusion of other liver disease			20. In your opinion, is this cryptogenic		
15 I. Alica and James Cardines and Ellison			cirrhosis (cirrhosis that fails to meet criteria for	NAE	LD
15. Is there evidence of brimary billary					
15. Is there evidence of primary biliary cirrhosis:			and without evidence of other form(s) of		
	(1	No 2)			
cirrhosis: (Yes 1)	(No 2)	and without evidence of other form(s) of liver disease): (Yes (1)	chro	
cirrhosis:	(No _2)	and without evidence of other form(s) of	chro	
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease:	(2)	and without evidence of other form(s) of liver disease): (Yes (1)	chro	
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (Yes (1) 1)		2)	and without evidence of other form(s) of liver disease): (Yes (1) 22	chro	
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease:		2)	and without evidence of other form(s) of liver disease): (Yes (1) 22 F. Other features	chro	
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (Yes (1) 1)		2)	and without evidence of other form(s) of liver disease): (Yes (1) 22 F. Other features 21. Other features (check all that apply)	chro	onic No 2)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (Yes (1) * Caution: Wilson's disease is exclusion 17. Features of chronic cholestatic liver		2)	and without evidence of other form(s) of liver disease): (Yes (1) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from	chro	onic No 2) 1
* Caution: Wilson's disease is exclusion * Caution: Wilson's disease is		2) No 2)	and without evidence of other form(s) of liver disease): Yes Yes 1 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa:	chro	onic No 2) 1
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (* 1) * Caution: Wilson's disease is exclusion * Caution: Wilson's disease is exclusion 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis:		2) No 2)	and without evidence of other form(s) of liver disease): (Yes (Yes 1)) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning:	chro	1) 1)
* Caution: Wilson's disease is exclusion * Caution: Wilson's disease is exclusion * Caution: Wilson's disease is exclusion 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis: b. Florid duct lesions:		2) No 2) 1) 1)	and without evidence of other form(s) of liver disease): Yes Yes 1 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning: d. Megamitochondria:	chro	1) 1) 1) 1)
cirrhosis: (Yes (1) 16. Is there evidence of Wilson's disease: (Yes (** 1) * Caution: Wilson's disease is exclusion * Caution: Wilson's disease is exclusion 17. Features of chronic cholestatic liver disease (check all that apply) a. Bile duct loss/infiltration/sclerosis: b. Florid duct lesions: c. Cholate stasis:		2) No 2) 1) 1) 1)	and without evidence of other form(s) of liver disease): Yes Yes 1 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning: d. Megamitochondria:	chro	1) 1) 1) 1)
* Caution: Wilson's disease is exclusion * Caution: Wilson's disease * Caution: Wilson's disease * Caution: Wilson's disease is exclusion * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply) * Caution: Cholestatic liver disease (check all that apply)		2) No 2) 1) 1) 1) 1)	and without evidence of other form(s) of liver disease): (Yes (Yes 1)) 22 F. Other features 21. Other features (check all that apply) a. Mallory's hyaline (r/o cholate stasis): b. Perisinusoidal fibrosis away from septa: c. Hepatocyte ballooning: d. Megamitochondria: e. Other (specify):	chro	1) 1) 1) 1)

G. Other comments

22. Other comments:

H. Administrative information

23. Study Pathologist PIN: ____ ___

24. Study Pathologist signature:

25. Clinical Coordinator PIN: ____ ___

26. Clinical Coordinator signature:

27. Date form reviewed:

day mon year

HI - Followup Medical History

Purpose: To record followup medical history information about the patient. When: f024, f048, f096, f144, and f192. Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview or chart review.

A. Center, visit, and patient identification D. Alcohol consumption (AUDIT-C) since the last visit 1. Center ID:

12. Is the patient age 8 or older:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

13. Since the last visit, how often have you had a drink containing alcohol:

Never	()
	16.
Monthly or less	(1)
Two to four times a month	(2)
Two to three times a week	(3)
Four or more times a week	(,)

14. Since the last visit, how many drinks 7. Study: NAFLD Database 1 containing alcohol have you had on a typical day when you are drinking:

h i 1

1 or 2	()
3 or 4	(1)
5 or 6	(2)
7 to 9	(3)
10 or more	()

15. Since the last visit, how often have you had six or more drinks on one occasion:

Never	(0
Less than monthly	(1)
Monthly	(2)
Weekly	(3)
Daily or almost daily	(4)

T. Contor ID.	
2. Patient ID:	
3. Patient code:	———

4. Visit date (date this form is initiated):

	day	mon	ye	ear	
code:			 		

6. Form & revision:

5. Visit

7 Ct 1	MACID Database 1

B. Interval identification

8. Date of last Followup Medical History form (if this is visit f024 then date of s1): day mon vear

9. Visit code of last Followup Medical History form (if this is visit f024 then s1):

C. NAFLD evaluation

10. Has the patient had a liver biopsy since the last visit:

$$\binom{\text{Yes}}{*}$$
 $\binom{\text{No}}{2}$

*Complete the Liver Biopsy Materials Documentation (SD) form.

11. Has the patient had an upper abdominal imaging study since the last visit:

$$\binom{\text{Yes}}{*}$$
 $\binom{\text{No}}{2}$

*Complete a Liver Imaging Studies Report (IR) form.

E. T	obacco cigarette smoking			r. Hepatic encephalopathy:	(1)
16. Since the last visit, have you smoked				s. Portal hypertension:	(1)
tobacco cigarettes regularly ("No" means		,		t. Hepatorenal syndrome:	(1)
	smoked less than 1 day per week on averag	g <i>e):</i> N	No	u. Hepatopulmonary syndrome:	(1)
	(1)	(2)	v. Short bowel syndrome:	(1)
	19.	-	J	w. Hemophilia (bleeding disorder):	(1)
17.	On average, how many days per week have you smoked cigarettes:			x. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:	(1)
18.	On the days that you smoked, about	# C	lays	y. Endocrine disease (hormonal abnormality):	(1)
	how many cigarettes did you smoke			z. Hepatocellular carcinoma:	(1)
	per day:			aa. Other malignancy (cancer):	(1)
	# cigarettes	per d	lay	ab. Peripheral neuropathy:	(1)
F. N	ledical history			ac. Seizure disorder or epilepsy:	(1)
19.	Since the last visit, has the patient been			ad. Drug allergies:	(1)
•	diagnosed with or treated for any of the			ae. Hypothyroidism:	(1)
	following (check all that apply; source of in tion can be interview and/or chart review)			af. Hypertension:	(1)
	a. Diabetes type 1:	(1)	ag. Cerebrovascular disease:	(1)
	b. Diabetes type 2:	(1)	ah. Dysbetalipoproteinemia:	(1)
	c. Gestational diabetes <i>(diabetes of pregnancy):</i>	(1)	ai. Hyperlipidemia (high cholesterol, high triglycerides):	(1)
	d. Hepatitis B:	(1)	aj. Pancreatitis:	(1)
	e. Hepatitis C:	(1)	ak. Cholelithiasis:	(1)
	f. Autoimmune hepatitis:	(1)	al. Coronary artery disease:	(1)
	g. Autoimmune cholestatic liver disorder		1.	am. Elevated uric acid such as gout:	(1)
	(PBC or PSC):	(1)	an. Kidney disease:	(1)
	h. Wilson's disease:	(1)	ao. Polycystic ovary syndrome:	(1)
	i. Alpha-1-antitrypsin (A1AT) deficiency:	(1)	ap. Sleep apnea (not breathing during sleep):	()
	j. Iron overload:	(1)	aq. Dermatologic disorders:	(1) 1)
	k. Drug induced liver disease:	(1)	ar. Myopathy:	(1)
	l. Gilbert's syndrome:	(1)	as. Myositis:	(1)
	m. Esophageal or gastric varices on endoscopy:	(1)	at. Major depression:	(1)
	n. Bleeding from varices:	(1)	au. Schizophrenia:	(1)
	o. Other gastrointestinal bleeding:	(1)	av. Bipolar disorder:	(1)
	p. Ascites:	(1)	aw. Obsessive compulsive disorder:	(1)
	q. Edema:	(1)	ax. Severe anxiety or personality disorder:	(1)
				ay. None of the above:	(1)

20.	Since the last visit, has the patient had surgery for any of the following (check all that apply)			G. Medication use26. Since the last visit, has the patient used		
	a. Stapling or banding of the stomach:	(1)	any antidiabetic medications (check all that apply):		
	b. Jejunoileal (or other intestinal) bypass:	(1)	a. Acarbose (Precose):	(1)
	c. Biliopancreatic diversion:	(1)	b. Acetohexamide (Dymelor):	(1)
	d. Other GI or bariatric surgery (specify):	(1)	c. Chlorpropamide (Diabinese):	(1)
				d. Glimepiride (Amaryl):	(1)
	e. None:	(1)	e. Glipizide (Glucotrol, Glucatrol XL):	(1)
21.	Since the last visit, has the patient received an organ, limb, or bone marrow			f. Glyburide (Micronase, DiaBeta, Glynase):	(1)
	transplant:			g. Insulin:	(1)
	$\binom{\mathrm{Yes}}{1}$	(No 2)	h. Metformin (Glucophage, Glucophage XR):	(1)
22.	Since the last visit, has the patient			i. Miglitol (Glycet):	(1)
	received total parenteral nutrition (TPN): Yes	. 1	No	j. Nateglinide (Starlix):	(1)
	$\binom{\mathrm{Yes}}{1}$	(No 2	k. Pioglitazone (Actos):	(1)
23.	23. Is the patient currently undergoing			I. Repaglinide (Prandin):	(1)
	evaluation for bariatric surgery:	N	No.	m. Rosiglitazone (Avandia):	(1)
	Yes (Yes	(No 2	n. Tolazamide (Tolinase):	(1)
24.	Since the last visit, has the patient been			o. Tolbutamide (Orinase):	(1)
	hospitalized:		.T	p. Other, (specify):	(1)
	$\binom{\mathrm{Yes}}{1}$	(2)			
	If Yes, specify reason:]		q. None of the above:	(1)
	specify reason			27. Since the last visit, has the patient taken any alcohol abuse (dependance or withdrawal) medications (check all that app	oly).	<u>:</u>
25.	Since the last visit, has the patient had any serious health problem not already			a. Chlordiazepoxide (Librium):	(1)
	reported:			b. Clorazepate dipotassium (Tranxene):	(1)
	$\binom{\operatorname{Yes}}{1}$	(1	No o	c. Diazepam (Valium):	(1)
	26.	<u> </u>		d. Disulfiram (Antabuse):	(1)
	If Yes, specify:	•		e. Hydroxyzine pamoate (Vistaril):	(1)
	specify			f. Naltrexone hydrochloride (Revia):	(1)
	эрсспу			g. Other, (specify):	(1)
				h. None of the above:	(

28. Since the last visit, has the patient taken any antihyperlipidemic medications (check all that apply):			30. Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing		
a. Atorvastatin (Lipitor):	(1)	medications (check all that apply):	,	,
b. Colestipol hydrochloride (Colestid):	(1)	a. Acetaminophen (Tylenol):	(1)
c. Clofibrate (Abitrate, Atromid-S,	,	,	b. Aspirin - 325 mg:	(1)
Claripex, Novofibrate):	(1)	c. Aspirin - 81 mg:	(1)
d. Gemfibrozil (Gen-Fibro, Lopid):	(1)	d. Celecoxib (Celebrex):	(1)
e. Fenofibrate (Tricor):	(1)	e. Ibuprofen (Advil, Motrin):	(1)
f. Fluvastatin sodium (Lescol):	(1)	f. Indomethacin (Indocin):	(1)
g. Lovastatin (Mevacor):	(1)	g. Naproxen (Aleve, Naprosyn):	(1)
h. Nicotinic acid (Niaspan):	(1)	h. Other, (specify):	(1)
i. Pravastatin sodium (Pravachol):	(1)			
j. Rosuvastatin (Crestor):	(1)	i. Other, (specify):	(1)
k. Simvastatin (Zocor):	(1)			
l. Other, (specify):	(1)	j. Other, (specify):	(1)
m. None of the above:	(1)	k. None of the above:		1)
any antiobesity medications (check all thata. Dexfenfluramine hydrochloride (Redux):	t app (oly): 1)	containing acetaminophen medication in the past 6 months (check all that apply)		
b. Fenfluramine hydrochloride			a. Darvocet:	(1)
(Pondimin):	(1)	b. Esgic - Plus:	(1)
c. Methamphetamine hydrochloride (Desoxyn, Gradumet):	(`	c. Fioricet:	(1)
	(1)	d. Lorcet:	(1)
d. Orlistat (Xenical):	(1)	e. Lortab:	(1)
e. Phendimetrazine tartrate (Adipost, Bontril):	(1)	f. Norco:	(1)
f. Phentermine hydrochloride (Adipex,		12	g. Percocet:	(1)
Fastin, Ionamin, Teramine):	(1)	h. Talacen:	(1)
g. Sibutramine hydrochloride	(`	i. Tylenol #3:	(1)
monohydrate (Meridia):	(1)	j. Tylenol #4:	(1)
h. Other, (specify):	(1)	k. Tylox:	(1)
			l. Vicodin:	(1)
i. Other, (specify):	(1)	m. Wygesic:	(1)
: None of the charge			n. Other, (specify):	(1)
j. None of the above:	(1)			
			o. None of the above:	(1)

32.	Since the last visit, has the patient taken any histamine H2 receptor antagonists/other gastrointestinal medications (check all that apply):		
	a. Cimetidine (Tagamet):	(1)
	b. Esomeprazole magnesium (Nexium):	(1)
	c. Famotidine (Pepcid):	(1)
	d. Lansoprazole (Prevacid):	(1)
	e. Nizatidine (Axid):	(1)
	f. Omeprazole (Prilosec):	(1)
	g. Ranitidine (Zantac):	(
	h. Ranitidine bismuth citrate (Tritec):	(1)
	, , ,	•	1)
	i. Antacids, (specify):	(1)
	j. Other, (specify):	(1)
	k. Other, (specify):	(1)
	1. None of the above:	(1)
33.	Since the last visit, has the patient taken any anticoagulant/antiplatelet medications (check all that apply):		
	a. Clopidogrel (Plavix):	(1)
	b. Dipyridamole:	(1)
	c. Heparin:	(1)
	d. Ticlopide (Ticlid):	(1)
	e. Warfarin (Coumadin):	(1)
	f. Other, (specify):	(1)
	g. Other, (specify):	(1)
	h. None of the above:	(1)

Since the last visit, has the patient taken any systemic corticosteroids (check all that apply):		
a. Betamethasone sodium (Celestone):	(1)
b. Cortisol:	(1)
c. Cortisone:	(1)
d. Dexamethasone (Decadron):	(1)
e. Hydrocortisone (Hydrocortone):	(1)
f. Methylprednisolone (Solu-Medrol):	(1)
g. Prednisolone (Prelone):	(1)
h. Prednisone:	(1)
i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort):	(1)
j. Other, (specify):	(1)
k. Other, (specify):	(1)
I. None of the above:	(1)

any cardiovascular/ medications (check	all that apply):			36. Since the last visit, has the patient taken any estrogen, progestin, hormone replacement therapy, or selective		
a. Amiodarone (Pacerone):		(1)	estrogen receptor modulators (check all that apply):		
b. Amlodipine besy	ylate (Norvasc):	(1)	a. Conjugated estrogen		
c. Atenolol (Tenor	min):	(1)	(Premarin/Prempro):	(1)
d. Benazepril (Lote	ensin):	(1)	b. Diethylstilbestrol and	(`
e. Captopril (Capor	ten):	(1)	methyltestosterone (Tylosterone):	(1)
f. Clonidine (Catap	ores):	(1)	c. Esterified estrogen (Estratab, Menest):	(1)
g. Digoxin (Lanoxi	in):	(1)	d. Estradiol (Estrace):	(1)
h. Diltiazem (Card	izem):	(1)	e. Ethinyl estradiol (Estinyl):	(1)
i. Doxazosin (Card	ura):	(1)	f. Fluoxymesterone (Android-F, Halotestin):	(1)
j. Enalapril (Vasoto	ec):	(1)	g. Levonorgestrel (Norplant):	(1)
k. Felodipine (Plen	dil):	(1)	h. Medroxyprogesterone (Cycrin,		12
I. Furosemide (Las	ix):	(1)	Provera):	(1)
m. Hydrochlorothi		,	`	i. Megestrol (Megace):	(1)
HydroDIURIL)		(1)	j. Methyltestosterone (Android):	(1)
n. Hydrochlorothia (Dyazide):	zide + triamterene	(1)	k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin):	(1)
o. Lisinopril (Prini	vil, Zestril):	(1)	l. Norethindrone (Micronor):	(1)
p. Losartan potassi	um (Cozaar):	(1)	m. Norgestrel (Ovrette):	(1)
q. Losartan potassi hydrochlorothia:		(1)	 n. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon, 	ì	,
r. Metoprolol (Lop	ressor):	(1)	Levlen, Levlite, Levora, Loestrin,		
s. Nifedipine (Adal	at, Procardia):	(1)	Lo-Ovral, Necon, Nelova, Nordette, Norethin, Norinyl, Ortho Cyclen,		
t. Perhexiline male	ate:	(1)	Ortho-Novum, Ortho Tri-Cyclen,		
u. Propranolol (Ind	leral):	(1)	Ovral, Tri-Levlen, Triphasil, Trivora, Zovia):	(1)
v. Quinapril (Accu	pril):	(1)	o. Oxandrolone (Oxandrin):	(1)
w. Terazosin (Hytr	in):	(1)	p. Oxymetholone (Anadrol):	(1)
x. Timolol maleate	(Blocadren):	(1)	q. Progesterone (Prometrium):	(1)
y. Valsartan (Diova	an):	(1)	r. Raloxifene (Evista):	(1)
z. Verapamil (Cala	n):	(1)	s. Tamoxifen (Nolvadex):	(1)
aa. Other, (specify)):	(1)	t. Other, (specify):	(1)
ab. Other, (specify)):	(1)	u. Other, (specify):	(1)
ac. None of the abo	ove:	(1)	v. None of the above:	(1)

				ad. Other, (specify):	(1)
	e. Other, (specify):	(₁)	ac. Other, (specify):	(1)
		(1)	ab. Zinc picolinate:	(1)
	c. Vitamin D: d. Vitamin E:	(1)	aa. Taurine:	(1)
	b. Vitamin C:	(1)	z. St. John's Wort:	(1)
	a. Vitamin B (any type):	(1)	y. Selenium:	(1)
	(check all that apply)	-	`	x. Saw palmetto:	(1)
40.	Which vitamins has the patient taken			w. S-adenylmethionine (SAM-e):	(1)
	41	. —	_	v. Potassium (any form):	(1)
	(Yes 1)	_ (_{_2})		u. N-acetyl-cysteine:	(1)
	vitamins other than multivitamins:	1	No .	t. Milk thistle:	(1)
	Since the last visit, has the patient taken			s. Magnesium:	(1)
	(1)	(2)	r. Lecithin:	(1)
	multivitamin regularly: (Yes (1)	_ 1	No 2	q. Glucosamine (any form):	(1)
	Since the last visit, has the patient taken a			p. Ginkgo biloba:	(1)
	j. Ivone of the doove.	(1)	o. Garlic:	(1)
	j. None of the above:	(1)	n. Flax seed oil:	(1)
	1. Outer, (speedy)).		17	m. Fish oil (any form):	(1)
	i. Other, (specify):	(1)	l. Echinacea:	(1)
	7(1 33)		17	k. Dichloroacetate:	(1)
	h. Other, (specify):	(1)	j. Coenzyme Q:	(1)
	g. Triamcinolone acetonide (Azmacort, Nasacort):	(1)	i. Cod liver oil:	(1)
	f. Mometasone furoate (Nasonex):	(1)	h. Choline + methionine + betaine + adenosine + pyridoxine (Epocler):	(1)
	e. Loratadine (Claritin):	(1)	g. Chondroitin (any form):	(1)
	Flovent):	(1)	f. Carnitine (any form):	(1)
	d. Fluticasone propionate (Flonase,	(1)	e. Calcium (any form):	(1)
	c. Budesonide (Pulmicort, Rhinocort):	(1)	d. Betaine (Cystadane):	(1)
	b. Beclomethasone dipropionate (Beclovent, Vanceril):	(`	c. Beta-carotene:	(1)
	a. Albuterol:	(1)	b. Alpha-tocopherol:	(1)
	(check all that apply):			a. Alpha-lipoic acid:	(1)
37.	Since the last visit, has the patient taken any allergy or asthma medications			41. Since the last visit, has the patient taken any supplements (<i>check all that apply</i>):		

 $\begin{pmatrix} 1 \end{pmatrix}$

ae. None of the above:

of the foll- supplement	last visit, has patient taken any owing medications or other hts/medications (record all other hts/medications):			H. Summary judgments about specific liver conditions (these judgments are to be made after all of the visit data are collected)				
a. Demec	a. Demeclocycline (Declomycin):			43. Subscores to compute Child-Pugh Turcotte score				
b. Divalp	roex (Depakote):	(1)	a. Rate the patient's ascites (check only one):				
c. Doxycy	veline (Monodox):	(1)	None (1)			
d. Isotreti	noin (Accutane):	(1)	Mild, easily managed (1) 2)			
e. Levoth	yroxine (Levoxyl, Synthroid):	(1)	Severe, refractory (3)			
-	onine (Cytomel):	(1)	b. Rate the patient's hepatic encephalopathy <i>(check only one)</i> :				
	rexate (Rheumatrex):	(1)	None (1)			
h. Minocy	ycline (Dynacin, Minocin):	(1)	Mild, easily managed	2)			
i. Oxytetr	acycline (Terramycin):	erramycin): Severe, refractory		Severe, refractory (3)			
j. Penicill	amine (Cuprimine, Depen):	(1)	I. Administrative information				
k. Tetracy	veline (Achromycin):	(1)					
l. Trientin	ne hydrochloride (Syprine):	(1)	44. Study Physician PIN:				
m. Ursod Ursod	eoxycholic acid (Actigall, Urso, iol):	(1)	45. Study Physician signature:				
n. Valpro	ate sodium (Depacon):	(1)					
o. Valpro	ic acid (Depakene):	(1)	46. Clinical Coordinator PIN:				
p. Other,	(specify):	(1)					
			12	47. Clinical Coordinator signature:				
q. Other,	(specify):	(1)					
r. Other,	(specify):	(1)	48. Date form reviewed:				
s. Other, ((specify):	(1)	day mon year				
t. Other, ((specify):	(1)					
u. None o	of the above:	(

IE - Interim Event Report

Purpose: To document (1) events that occur after registration but before enrollment, or between regular followup visits, that impact on the patient's participation in NAFLD Database (eg, mild or moderate liver biopsy complications), or (2) adverse events associated with study participation that do not meet the criteria for Serious Adverse Event Report (AN), or (3) other event that clinical center staff feel should be reported now rather than wait until the next followup visit and that is not recorded on another NAFLD Database form.

When: As needed; use visit code n. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code n for first event, n1 for second event, etc.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 21) and the severity code (item 22) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Documents and then click on General Documents. Fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher (Fax 410-955-0932).

NASH CRN Data Coordinating Center telephone number: (410) 955-8175.

			` '		
A. Center, patient, and	visit identificat	ion	C. Patient information		
1. Center ID:			9. Date enrolled in NAFI tient is not yet enrolled	LD Database <i>(ed):</i>	nter n if pa-
2. Patient ID:				mon	year
3. Patient code:			10. Gender:		
4. Date of report:			Male Female		$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$ $\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
day	mon	year	11. Age at time of event:		years
5. Visit code:	<u>n</u>		D. Event description		J
6. Form & revision:	<u>_i</u>	<u>e</u> 1	12. Date event started:		
7. Study:	NAFLD I	Database 1		mon	year
B. Visit interval identif	ication		13. Is the event associated PIVENS study drug us		
8. Most recently compor followup)	oleted visit (scree	ening		Yes () (No 2) [16.]
a. Date:day	mon mon	year	14. Is the event due to the study drug:	pioglitazone-se	eries
b. Visit code:			Definitely yes		(1)
			Probably yes		(2)
			Possibly yes		$\begin{pmatrix} & & \\ & & \end{pmatrix}$
			Probably no		(4)
			Definitely no		$\begin{pmatrix} & & \\ & & 5 \end{pmatrix}$

nt due to the vitamin E-series			20. Describe event:
yes	(1)	
yes	(2)	
yes	(3)	
no	(4)	
y no	(5)	
nt associated with prior TONIC g use:	1		
(Yes 1) <u>1</u>	9.	No 2)	21. Short name for event if applicable (short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents):
nt due to the metformin-series g:			Not applicable $\begin{pmatrix} & & & & & & & & & & & & & & & & & & $
yes yes	(1)	
yes	(2)	
yes	(3)	22. Severity grade (severity grades are listed in the
no	(4)	CTCAE v3.0 document available at
y no	(₅)	www.nashcrn.com; click on Documents and then click on General Documents; use Serious Adverse
nt due to the vitamin E-series			Event Report (AN) to report serious and unex- pected adverse events or call the DCC if unsure what to do:
/ yes	(1)	Not applicable (0)
yes	(2)	Grade 1 - Mild (1)
yes	(3)	Grade 2 - Moderate (2)
no	(4)	Grade 3 - Severe (3)
y no	(₅)	Grade 4 - Life threatening or disabling Grade 5 - Death $(*_5)$
event (check all that apply)			
l anesthesia:	(1)	*Complete and key Death Report (DR) form.
ation related event:	(1)	23. Date event resolved (enter n if event is not yet
procedure related event:	(1)	resolved):
nteractions:	(1)	day mon year
ning of a co-morbid illness:	(1)	24. What action was taken:
reported symptom of oxicity:	(1)	24. What action was taken.
lycemia:	(1)	
nset diabetes:	(1)	
ncy (patient):	(1)	
specify):	(1)	
nset o	liabetes: patient):	liabetes: (patient): (liabetes: $\binom{1}{1}$ patient): $\binom{1}{1}$

Patient ID:				
-------------	--	--	--	--

25.	Other comm	ents on ev	vent:		
E. A	dministrativ	e inform	ation		
26.	Clinical Coo	rdinator F	PIN:		
27.	Clinical Coc	ordinator s	ignature:		
28.	Study Physic	cian PIN:	_		
29.	Study Physic	cian signa	ture:		
30.	Date form re	eviewed:			
		day	mon	 yea	ar

Key this form and fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious events so that we assure appropriate and timely study wide review. The received reports will be reviewed by Jeanne Clark, the Safety Officer, for appropriate further review by the Steering Committee and Data and Safety Monitoring Board.

IR - Liver Imaging Studies Report

Purpose: To record liver imaging study results. **When:** Visits s2, f024, f048, f096, f144, and f192.

Administered by: Clinical Coordinator.

Instructions: Complete this form at each of the visits listed above if the Baseline Medical History (BG) or Followup Medical History (HI) form says that liver imaging study was obtained in the specified period. The form will allow you to skip out of sections that are irrelevant to your patient. What you will report at each visit are the results of the most recent scan of each type done in the year prior to screening (visit s2) or in the period since the prior study visit (after enrollment). These will likely be standard of care scans with results obtained via medical records. In each case, answer the items based on review of the report; the Study Physician must review and approve the findings recorded on this form. Liver imaging studies available at baseline and during followup should be reported on this form even if the patient has definite NAFLD or cryptogenic cirrhosis by histology.

A. Center, patient, and visit identification	10. Findings suggestive of NAFLD, cryptogenic cirrhosis, or others of				
1. Center ID:	significance (check all that apply)				
2 Patient ID.	a. Fatty infiltration:	(1)		
2. Patient ID:	b. Cirrhosis:	(1)		
3. Patient code:	c. Hepatomegaly:	(1)		
	d. Hepatic mass:	(1)		
4. Date of visit:	e. Intrahepatic biliary dilatation:	(1)		
day mon year 5. Visit code:	f. Extrahepatic biliary dilatation:	(1)		
	g. Gallstones/cholelithiasis:	(1)		
6. Form & revision:i _ r1	h. Gall bladder polyps:	(1)		
7. Study NAFLD Database 1	i. Cholecystectomy:	(1)		
7. Study: NAFLD Database 1	j. Splenomegaly:	(1)		
B. Upper abdominal ultrasound	k. Ascites:	(1)		
8. Did the patient have an upper abdominal ultrasound in the past year (<i>screening</i>)/ since the last visit (<i>followup</i>):	I. Other features of portal hypertension <i>(specify):</i>	(1)		
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	m. Other abnormality (specify):	(
9. Date of most recent upper abdominal ultrasound:					
day mon year	n. None of the above:	(1)		

C. Upper abdominal CT scan

11. Did the patient have an upper abdominal CT scan in the past year (screening)/ since the last visit (followup):

(Y	es 1	(No
		14.

1)

12. Date of most recent upper abdominal CT scan:

day	mon	year

13. Findings suggestive of NAFLD, cryptogenic cirrhosis, or others of significance (check all that apply)

a. Fatty infiltration:	(
b. Cirrhosis:	(
c. Henatomegaly:	(

d. Hepatic mass:	(
e. Hepatic hemangioma:	(

f. Hepatic cyst:	(1.

g. Intrahepatic biliary		
dilatation:	(1)

h. Extrahepatic biliary		
dilatation:	(1

i. Gallstones/cholelithiasis:		1
j. Gall bladder polyps:	(1

-		,	12
k.	Cholecystectomy:	(1)

l. Splenomegaly:	(1)
m. Ascites:	(1)

n.	Other features of portal		
	hypertension (specify):	(1)

0.	Other abnormality (specify):	(1)

•		
p.	None of the above:	

D. Upper abdominal MRI

14. Did the patient have an upper abdominal MRI in the past year (*screening*)/since the last visit (*followup*:



15. Date of most recent upper abdominal MRI:

_		
day	mon	year

16. Findings suggestive of NAFLD, cryptogenic cirrhosis, or others of significance (check all that apply)

significance (check all that apply)	
a. Fatty infiltration:	(

b. Cirrhosis:	(1)
c. Hepatomegaly:	(1)

dilatation:	(1)
i. Splenomegaly:	(1)

k. Other features of portal		
hypertension (specify):	(1)

l.	Other abnormality (specify):	(1)

m. None of the above:	()
m. None of the above.	(1

1)

Patient ID:	 	

•			. •		
н,	Adr	ninisti	rafive	intor	mation

day

17.	Study Physician PIN:
18.	Study Physician signature:
19.	Clinical Coordinator PIN:
20.	Clinical Coordinator signature:
21.	Date form reviewed:

mon

year

LD – Lifetime Drinking History (Skinner)

Keyed: ()

Purpose: To obtain quantitative indices of the patient's alcohol consumption patterns from the onset of regular drinking

When: Visit s1. If more than one LD form is needed, use visit code "n" on the second LD form.

Administered by: Clinical Coordinator.

Respondent: Patient, 18 years of age or older, without help from spouse or family.

Instructions: In addition to actual consumption levels (quantity), attention is focused upon the frequency of use, variability in consumption, types of beverages, life events that mark a change in drinking pattern, solitary versus social drinking, and time of day when alcohol is consumed. Flash Card #15, Drink Equivalents, may be used with this interview.

The interviewer begins by recording the patient's alcohol consumption behavior during the first year that he/she drank on a regular basis (at least one drink per month). Then, the patient is asked to think of when his/her drinking behavior changed in any appreciable way. In a chronological fashion, the interviewer traces the patient's alcohol consumption behavior from the age of first regular drinking to the present. Flash Card #16, Patterns of Alcohol Intake, provides sample language for the interviewer. Each LD form allows for describing six drinking phases. Use a second LD form (visit code "n") if needed to describe additional drinking phases. If this is the second LD form, skip sections B and C and start with item 20.

The interview takes approximately 20 minutes to complete. It is best given after a reasonable degree of rapport has been established, whereby the patient will feel more at ease and talk openly. Other, considerable probing and cross-referencing of facts is necessary to help in accurate recall. All information should be recorded under the appropriate heading on the LD form.

Α.	Center.	natient.	and	visit	iden	tificatio	n

1.	Center ID:				
2.	Patient ID:				
3.	Patient code:				
4.	Date of visit (date p	atient co	mpletea	l the for	m):
	a	mon	<u> </u>	y	ear
5.	Visit code:				
6.	Form & revision:		_l_	d	_1_
7.	Study:	N/	AFLD	Databa	ase <u>1</u>

B. Lifetime alcohol consumption

8. Over the course of your lifetime have you ever had at least one drink of alcohol, beer, liquor, wine, or wine coolers, per month during a 12-month time period, or at least three drinks per day for at least three consecutive days (over a regular period of time):



Patient ID:		

C. First phase

Read as written: "Now, I am going to ask you about your drinking pattern during the first year that you began to have at least one drink per month until your drinking behavior was different in a significant way from this time."

9. How old were you when you began regular drinking:

a. Years:

yrs

b. Months:

mos

10. How old were you at the end of first stage:

a. Years:

yrs

b. Months:

mos

11. During the first stage, how many drinks would you have on average per occasion (*drinking day*):

drinks

12. How many days per month would you generally drink at this level:

days

13. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

14. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%):

Beer

%

Liquor

9/0

Wine

9/0

15. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent (1)
Occasional (less than 15 days) (2)
Weekend mainly (3)

Binge (at least 3 days heavy drinking)
Frequent (15 days or more per month)

16. Did any important event or events occur during

this period that altered your usual drinking habits:

Yes
No
(1) (2)

18.

17. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

Positive Negative Neutral Marital/family . . (3) Work (2) 3) School (c. 2) 3) Medical (1) 2) 3) Residence (e 1) f. Legal/jail (Financial (g. 1) Peer group (h. 1) Drug abuse (i. 1) 3) j. Treatment (2) 1) 3) Death (k. 1) 2) 3) Emotional (

18. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%):

Alone

With others

Patient ID:		

19. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 %	
Afternoon	 %	
Evening	 0/2	

D. Subsequent phase

20. Read as written: "We have just discussed your drinking habits at the point when you first began to drink regularly. Now I want you to think to when your drinking behavior was different in a significant way from this time. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



21. How old were you at the beginning of this phase:

a.	Years:	yrs
b.	Months:	mos

22. How old were you at the end of this phase:

a.	Years:	yrs
b.	Months:	mos

23. During this phase, how many drinks would you have on average per occasion (*drinking day*):

drinks

24. How many days per month would you generally drink at this level (write "m" if not drinking):

# days	

25. What is the most or maximum number of drinks you would have in any one day:

#	drinks	

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

26. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

Beer	 %	
Liquor	 %	
Wine	 	

27. How would you rate your usual style of drinking during an average month *(check the appropriate category)*:

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	(5)

28. Did any important event or events occur during this period that altered your usual drinking habits:



29. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

-33	7.	Positi	ive	Nega	ative	Net	ıtral
a.	Marital/family	(1)	(2)	(3)
b.	Work		1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
g.	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse	(1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
1	Emotional	(.)	(.)	(Â

Patient ID:		

30.	What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):
	Alone

31.	During what time of the day would you do most of
	your drinking? Could you give me the percentage
	of time during the evening, afternoon and morning
	(record the relative percentages of morning,
	afternoon and evening; this section should add up
	to 100%; if not drinking, percentages should all

Morning	 %	
Afternoon	 %	
Evening	 <u></u>	

E. Next subsequent phase

With others

be "000"):

32. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at a subsequent phase. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":

Yes

No

Yes		No	
(1)	(2)
	81		

%

- **33.** How old were you at the beginning of the phase:
 - **a**. Years:

 yrs **b**. Months:

 mos
- **34.** How old were you at the end of this phase:

10 W	old were you at the end of	uns phase.
a.	Years:	yrs
b.	Months:	mos

35. During this phase, how many drinks would you have on average per occasion (*drinking day*):

drinks

36. How many days per month would you generally drink at this level (write "m" if not drinking):

days

37. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

38. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

39. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent (1)
Occasional (less than 15 days) (2)
Weekend mainly (3)
Binge (at least 3 days heavy drinking) (4)
Frequent (15 days or more per month) (5)

Patient ID:		

40. Did any important event or events occur during this period that altered your usual drinking habits:

Y	es '	N	No
(1)	(2)
	42] ←	

41. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Neg	ative	Ne	utral
a.	Marital/family	. (1)	(2)	(3)
b.	Work	. (1)	(2)	(3)
c.	School	. (1)	(2)	(3)
d.	Medical	. (1)	(2)	(3)
e.	Residence	. (1)	(2)	(3)
f.	Legal/jail	. (1)	(2)	(3)
g.	Financial	. (1)	(2)	(3)
h.	Peer group	. (1)	(2)	(3)
i.	Drug abuse	. (1)	(2)	(3)
j.	Treatment	. (1)	(2)	(3)
k.	Death	. (1)	(2)	(3)
l.	Emotional	. (1)	(2)	(3)

42. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):

Alone	 %	
With others	 %	

43. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 %	
Afternoon	 0%	
Evening	 %	

F. Next subsequent phase

44. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



45. How old were you at the beginning of the phase:

a.	Years:	
		yrs
b.	Months:	

46. How old were you at the end of this phase:

Vanra.

а.	rears.	yrs
b.	Months:	

47. During this phase, how many drinks would you have on average per occasion (*drinking day*):

# drinks	

48. How many days per month would you generally drink at this level (write "m" if not drinking):

# days	

49. What is the most or maximum number of drinks you would have in any one day:

#	drinks	

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

Patient ID:		

50.	What type of beverage would you usually
	consume in an average month (record the relative
	percentages of beer, liquor or wine; this section
	should add up to 100%; if not drinking,
	percentages should all be "000"):

Beer	 %	
Liquor	 0/0	
Wine	 <u>%</u>	

51. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	(5)

52. Did any important event or events occur during this period that altered your usual drinking habits:

Yes No

Yes		N	lо
(1)	(2)
	54] ←	

53. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Neg	ative	Ne	utral
a.	Marital/family	(1)	(2)	(3)
b.	Work	(1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
\mathbf{g} .	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse	(1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
l.	Emotional	(1)	(2)	(3)

54. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):

Alone	 %	
With others	 <u>%</u>	

55. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	%
Afternoon	
Evening	

G. Next subsequent phase

drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":

Y	es	N	lо
(1)	(2)
	81] ←	

57. How old were you at the beginning of the phase:

a.	Years:	
		yrs
b.	Months:	

58. How old were you at the end of this phase:

a.	Years:	
		yrs
b.	Months:	
		mos

Patient ID:		

59.	During this phase, how many drinks we have on average per occasion (drinking)	# drinks	65.	What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no	
60.	How many days per month would you drink at this level (write "m" if not dr			effect):	
61.	What is the most or maximum number you would have in any one day: (Note: This is the maximum number to patient actually would drink, not an endis/her potential capacity.)	# drinks		a. Marital/family . (b. Work (c. School (d. Medical (e. Residence (f. Legal/jail (g. Financial (h. Peer group (i. Drug abuse (k. Death (Desitive Negative Neutral 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3)
62.	What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"): Beer		66.	I. Emotional $\binom{1}{1}$ $\binom{2}{2}$ $\binom{2}{1}$	
	Liquor	%		Alone With others	
63.	How would you rate your usual style of drinking during an average month (check the appropriate category); Abstinent Occasional (less than 15 days) 67. During what time of the day we your drinking? Could you give of time during the evening, after (record the relative percentage afternoon and evening; this see to 100%; if not drinking, percentage be "000"):		u give me the percentage g, afternoon and morning entages of morning, his section should add up		
	Weekend mainly Binge (at least 3 days heavy drinking Frequent (15 days or more per month)	$\begin{pmatrix} & & & \\ & & & \\ & & & \\ \end{pmatrix} \qquad \begin{pmatrix} & & \\ & & & \\ \end{pmatrix}$		Morning	
64.	Did any important event or events occ this period that altered your usual driv	nking habits:		Afternoon	
	Ye (es No 1) (2) 66.		Evening	%

Patient ID:		

H. Next subsequent phase

68. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":

69.	How old	d were	vou	at the	begin	ning	of the	phase

a. Years:

yrs

b. Months:

mos

70. How old were you at the end of this phase:

a. Years:

yrs

b. Months:

mos

71. During this phase, how many drinks would you have on average per occasion (*drinking day*):

drinks

72. How many days per month would you generally drink at this level (write "m" if not drinking):

days

73. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

4. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

75. How would you rate your usual style of drinking during an average month (*check the appropriate category*);

Abstinent
Occasional (less than 15 days)
Weekend mainly
Binge (at least 3 days heavy drinking)
Frequent (15 days or more per month)

76. Did any important event or events occur during this period that altered your usual drinking habits:



77. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

	Pos	sitive	Neg	gative	Ne	utral
a.	Marital/family (1)	(2)	(3)
b.	Work (1)	(2)	(3)
c.	School (1)	(2)	(3)
d.	Medical (1)	(2)	(3)
e.	Residence (1)	(2)	(3)
f.	Legal/jail (1)	(2)	(3)
g.	Financial (1)	(2)	(3)
h.	Peer group (1)	(2)	(3)
i.	Drug abuse (1)	(2)	(3)
j.	Treatment (1)	(2)	(3)
k.	Death (1)	(2)	Ì	3)
l.	Emotional (1)	Ì	2)	Ì	2)

Patient ID:		

78.	What percentage of time we and what percentage of the other person (record the rei "Alone" and "With others" add up to 100%; if not drin should all be "000"):	time with at leas lative percentage "; this section sho	t one es of ould
	Alone		
		%	
	With others		
		%	
79.	During what time of the day your drinking? Could you a of time during the evening, (record the relative percent afternoon and evening; this to 100%; if not drinking, pe be "000"):	give me the perce afternoon and m tages of morning section should a	entage orning g, add up
	Morning		
	Afternoon		
	Evening		
. Nu	mber of phases		
80.	Are there any additional sul	yes (* 1)	No (₂)
	* If yes, complete a second Skip sections B and C on se		
J. Adr	ministrative information		
81.	Clinical Coordinator PIN:		
82.	Clinical Coordinator signat	ure:	
83.	Date form reviewed:	_	
	day mon		ar

A

LP – Symptoms of Liver Disease (Children)

Purpose: To obtain the patient's view of his/her liver disease symptoms.

When: Visits s1, f048, f096, f144, and f192.

Administered by: Self-administered (age 13-17), interview er administered (age 2-12). Clinical Coordinator must be available to answer questions and review for completeness.

Respondent: Patient, age 2 through 17. Patient age 13 or older should complete the form without help from family. Clinical Coordinator/parent should assist patient age 2-12.

Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-4. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in the completion of the form, and then should complete pages 2-4. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should then complete section B below.

Ce	nter, patient, and vi	sit identification		ministrative information o be completed by Clinical Coordinator afi	tor	
1.	Center ID:			rvey is completed.)	er	
2.	Patient ID:		8.	How was the questionnaire completed:		
3.	Patient code:			Self-administered by patient/parent	(1)
4.	Date of visit:			10	<u>J.</u>	
		mon year		Interview in English Interview with translator	(2) 3)
5.	Visit code:		9.	Who was the respondent (check all that a	<i>ppl</i> y):	
6.	Form & revision:	<u>l p 1</u>		a. Patient:b. Patient's mother or female	(1)
7.	Study:	NAFLD Database 1		guardian:c. Patient's father or male guardian:d. Other (specify):	((1) 1) 1)
				specify		—
			10.	Clinical Coordinator a. PIN: b. Signature:		
			11.	Date form reviewed:		
				day mon	year	

Affix label here
Patient ID:
Patient code:
Visit code:

Symptoms of Liver Disease

Instructions: People with liver disease may or may not have symptoms, such as pain over the liver area (under your ribs, right of your belly), feeling sick to your stomach, poor appetite (not feeling hungry), itching, or tiredness. In this questionnaire, we are trying to identify what symptoms you have, how severe they are, and how much they affect you.

(Items 1-11 are reserved for clinical center use.)

12. During the last month, how much have you been bothered by the following:

Circle one for each symptom

Degree of bother

		None at all	A little bit	Medium	Quite a bit	Extremely
a.	Pain over liver (pain under ribs, right of your belly)	1	2	3	4	5
b.	Nausea (sick to stomach)	1	2	3	4	5
c.	Poor appetite (not hungry)	1	2	3	4	5
d.	Fatigue	1	2	3	4	5
e.	Weight loss	1	2	3	4	5
f.	Diarrhea (watery poop)	1	2	3	4	5
g.	Muscle aches or cramps	1	2	3	4	5
h.	Muscle weakness	1	2	3	4	5
i.	Headaches	1	2	3	4	5
j.	Easy bruising ("black and blue" marks are easy to get)	1	2	3	4	5
k.	Itching	1	2	3	4	5
1.	Irritability (get mad easily)	1	2	3	4	5
m.	Depression/sadness	1	2	3	4	5
n.	Trouble sleeping	1	2	3	4	5
0.	Trouble concentrating (trouble with attention, thinking about one thing at a time)	1	2	3	4	5

Affix label here
Patient ID:
Patient code:
Visit code:

Circle one for each symptom

Degree of bother

	None at all	A little bit	Medium	Quite a bit	Extremely
p. Jaundice (yellow color to skin, eyes, etc)	1	2	3	4	5
q. Dark urine (dark pee)	1	2	3	4	5
r. Swelling of ankles	1	2	3	4	5
s. Swelling of abdomen (belly swells up)	1	2	3	4	5

13. Which of the following best describes how tired you feel and how your tiredness affects you (choose only one):

Circle one

		ircie on
	I feel normal and am not tired (If this is how you feel, please circle "1" and g to item number 17 – Thank you!)	
	I feel tired some of the time, but can do what I want to do without trouble I feel tired, and do what I want but with trouble I feel tired and it keeps me from doing what I want to do	2
14.	How often are you bothered by being tired (choose only one):	
	All day, every day Part of the day, every day At least part of several days a week At least part of one day a week Not as much as above	2 3 4
15.	Are you tired (choose only one):	
	When you wake up in the morning Or does it come on with the day Or does it have no time pattern	. 2
16.	Do you feel more tired the day after you exercise or have a lot of activity:	
	Yes	. 1

Affix label	here
Patient ID:	
Patient code:	
Visit code:	

17. In general, how have you felt overall in the past month:

Very good	1
Good	2
Fair	3
Poor	4
Awful	5

18. Today's date:

Thank you for completing this questionnaire.

LQ - Symptoms of Liver Disease

Purpose: To obtain the patient's view of his/her liver disease symptoms.

When: Visits s1, f048, f096, f144, and f192.

Administered by: Self-administered during the visit, but Clinical Coordinator must be available to answer questions and review for completeness.

Respondent: Patient, 18 years of age or older.

Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-4. The patient should complete pages 2-4 during the visit. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should then complete section B below.

A. Ce	enter, patient, and vi	sit identification		Iministrative info		ator after
1.	Center ID:		,	(To be completed by Clinical Coordinator survey is completed.)		
2.	Patient ID:		8.	Clinical Coordina a. PIN:	ntor	
3.	Patient code:			b . Signature	:	
4.	Date of visit:					
	day -	mon year	9.	Date form review	red:	
5.	Visit code:			day -	mon	year
6.	Form & revision:	<u>l q</u> _	1_			
7.	Study:	NAFLD Databas	e <u>1</u>			

Affix i	label here
Patient ID:	
Patient code:	
Visit code:	

Symptoms of Liver Disease

Instructions: People with liver disease may or may not have symptoms, such as pain over the liver area (right upper quadrant), nausea, poor appetite, itching, tiredness, or fatigue. In this questionnaire, we are trying to identify what symptoms you have, how severe they are, and how much they affect your life style.

(Items 1-9 are reserved for clinical center use.)

10. During the last month, how much have you been bothered by the following: *Circle one for each symptom*

	Degree of bother				
	None at all	A little bit	Moderately	Quite a bit	Extremely
a . Pain over liver (right upper quadrant)	1	2	3	4	5
b . Nausea	1	2	3	4	5
c. Poor appetite	1	2	3	4	5
d. Fatigue	1	2	3	4	5
e. Weight loss	1	2	3	4	5
f. Diarrhea	1	2	3	4	5
g. Muscle aches or cramps	1	2	3	4	5
h. Muscle weakness	1	2	3	4	5
i. Headaches	1	2	3	4	5
j . Easy bruising	1	2	3	4	5
k. Itching	1	2	3	4	5
I. Irritability	1	2	3	4	5
m. Depression/sadness	1	2	3	4	5
n. Trouble sleeping	1	2	3	4	5
o. Trouble concentrating	1	2	3	4	5
p . Jaundice (yellow color to skin, eyes, etc)	1	2	3	4	5
q. Dark urine	1	2	3	4	5
r. Swelling of ankles	1	2	3	4	5
s. Swelling of abdomen	1	2	3	4	5

Affix label here				
Patient ID:				
Patient code:	<u> </u>			
Visit code:				

11. Which of the following best describes your level of fatigue and the effects of your fatigue (*choose only one*):

		Circle one
	I feel completely normal and have no fatigue (circle "1" and go to item # 16)	1
	I have some fatigue, but I can do what I want to do without difficulty	2
	I have fatigue, and I do what I want to do but with difficulty	
	I have fatigue and it keeps me from doing what I want to do	
	I have fatigue that prevents me from working	
	I have fatigue that prevents me from working and requires that	
	I have assistance to carry out normal activities of living	6
	I am worse off than any of these statements suggest	7
12.	How frequently are you bothered by fatigue (choose only one):	
	All day, every day	1
	Part of the day, every day	
	At least part of several days a week	3
	At least part of one day a week	
	Less frequently	5
13.	Is your fatigue typically present (choose only one):	
	When you wake up in the morning	
	Or does it come on with the day	2
	Or does it have no time pattern	
14.	Is your fatigue typically worse the day after a period of extra activity or e	xercise:
	Yes	1
	No	2

Affix label here
Patient ID:
Patient code:
Visit code:
L

15. Do you believe that your fatigue is due to your liver problem (as opposed to something else, like not getting enough sleep, depression or being out of shape):

	Circle one
	Yes 1
	No
16.	In general, how have you felt overall in the past month:
	Very good
	Good
	Fair
	Poor4
	Awful
17.	Today's date:

Thank you for completing this questionnaire.

LR - Laboratory Results - Tests Done During Screening and Followup

Purpose: To record archival and current laboratory test results for tests done during both screening and followup. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Study Physician (adult hepatologist, pediatric hepatologist, or pediatrician) and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat test if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Please note that the units 10^3 cells/ μ L, 1000 cells/ μ L, and 10^9 cells/L are equivalent. Call the DCC if you have questions about conversion or how to record a value. Staple the lab report to the back of this form. If your lab reports values electronically, print a copy of the results and staple the report to the back of this form.

A. Center, patient, and visit identification	C. Chemistries and HbA1c			
1. Center ID:	13. Date of blood draw for chemistries:			
2. Patient ID:	Date must be within the requ	in the time window		
3. Patient code:	for the followup visit (check the visit time window guide).	patient s Database		
4. Date of visit (date form was initiated):	14. Sodium:*			
day mon year		meq/E		
5. Visit code:	15. Potassium:*	mEq/L		
6. Form & revision: _1r3_	16. Chloride:*			
		mEq/L		
7. Study: NAFLD Database 1	17. Bicarbonate:*	mEq/L		
B. Hematology	18. Calcium:*	· •		
8. Date of blood draw for complete blood		mg/dL		
count:	19. Phosphate:*			
day mon year Date must be within the required time window: within 6 months of screening or in the time window	20. Blood urea nitrogen (BUN):	mg/dL		
for the followup visit (check the patient's Database visit time window guide).	21. Creatinine:	· •		
9. Hemoglobin:	22. Uric acid:	mg/dL		
10. Hematocrit:	* Optional: If not done, enter	mg/dL "m".		
%	23. Date of blood draw for HbA1c	:		
11. White blood cell count (WBC):				
$\frac{10^{3} \text{ cells/} \mu \text{L or } 10^{9} \text{ cells/} \text{L}}{10^{9} \text{ cells/} \text{L}}$	aay mon Date must be within the requ within 3 months of screening or for the followup visit (check the	tired time window:		
12. Platelet count:	visit time window guide).			

cells/ μL

		Patient ID:	
HbA1c:		36. Date of blood draw for alpha feto protein:	
iver panel and alpha feto pro	otein	day mon yea Date must be within the required time win within 6 months of screening or in the time win	dow:
Date of blood draw for liver pa	nnel:	for the followup visit (check the patient's Data visit time window guide). Record "m" if tes done.	base
day mor Date must be within the requ within 6 months of screening o for the followup visit (check the	uired time window:	37. Alpha feto protein:	
visit time window guide).		ng/mL	
Bilirubin (total):	•	E. Fasting lipid profile	
Bilirubin (direct):	mg/dL	Fasting is defined as nothing by mouth exwater for greater than or equal to 12 hours per to blood draw.	ccept prior
Aspartate aminotransferase (A	mg/dL ST)	38. Date of blood draw for fasting lipid profile:	
a. Upper limit of normal:b. Lower limit of normal:		day mon yea Date must be within the required time win within 6 months of screening or in the time win for the followup visit (check the patient's Data visit time window guide).	dow: 1dow
		a. Triglycerides:	
Alanine aminotransferase (AL	T)	b. Total cholesterol:	
a. Upper limit of normal:	U/L	mg/dL	
	U/L	c. HDL cholesterol: mg/dL	
b. Lower limit of normal:		d. LDL cholesterol: mg/dL	
Alkaline phosphatase		F. Fasting glucose and insulin	
a. Upper limit of normal:		Fasting is defined as nothing by mouth exwater for greater than or equal to 12 hours p	cept prior
b. Lower limit of normal:		to blood draw.	
Gamma glutamyl transferase (GGT):	39. Date of blood draw for fasting glucose and insulin levels:	
T. 1		day mon yea Date must be within the required time win	dow:
Total protein:		within 6 months of screening or in the time win for the followup visit (check the patient's Data visit time window guide).	

Form LR			
Revision ?	3 (27	Jan	06

24. HbA1c:

D. Liver panel and alpha feto protein

25. Date of blood draw for liver panel:

28. Aspartate aminotransferase (AST)

29. Alanine aminotransferase (ALT)

31. Gamma glutamyl transferase (GGT):

35. International normalized ratio (INR):

30. Alkaline phosphatase

32. Total protein:

34. Prothrombin time (PT):

33. Albumin:

26. Bilirubin (total):

27. Bilirubin (direct):

 $\mu U/mL$

a. Serum glucose:

b. Serum insulin:

Patient ID:		

day

40. Study Physician PIN:

41. Study Physician signature:

42. Clinical Coordinator PIN:

43. Clinical Coordinator signature:

44. Date form reviewed:

mon

year

LS - Laboratory Results -Tests Done only During Screening

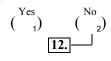
Purpose: To record archival and current results of laboratory tests done only at screening.

Administered by: Study Physician (adult hepatologist or pediatrician) and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have questions about conversion or how to record a value. If is checked for any item, you do not need to complete the rest of the form and the form may not be keyed.

A. Center, patient, and visit identification	c. Hepatitis B surface antibody (anti-HBs)*:
1. Center ID:	Positive (,)
	Negative (2)
2. Patient ID:	d. Hepatitis C antibody (anti-HCV) (indicate result as negative if EIA is
3. Patient code:	positive but RIBA is negative or if RIBA is indeterminate but HCV RNA is negative):
4. Date of visit:	Positive (
	Negative (2)
day mon year	e. Hepatitis C virus RNA:
5. Visit code:s1	Positive (1)
	in the second se
6. Form & revision:	Negative (₂)
WATER DOLLAR	Not available $\binom{3}{3}$
7. Study: NAFLD Database 1	f. Hepatitis A virus antibody (anti-HAV, total):
B. Screening etiologic tests	Positive (1)
	Negative (2)
8. Date of blood draw for serological assays to exclude viral causes of chronic liver	Not available $\begin{pmatrix} & & & \\ & & & \end{pmatrix}$
disease:	C. Iron
day mon year Repeat if date is greater than 5 years prior to screening.	9. Date of blood draw for iron overload screening:
If the patient is judged by Study Physician to have a high-risk lifestyle, repeat if date is greater than 6 months prior to screening. *Record as "m" if	day mon year Repeat if date is greater than 5 years prior to screening.
test is not done.	a. Iron:
a. Hepatitis B surface antigen (HBsAg):	$\mu \mathrm{g}/\mathrm{d}\mathrm{L}$
Positive (1)	b. Total iron binding capacity: μg/dL
Negative (₂)	μβαυ
b. Hepatitis B core total antibody	c. Ferritin:
(anti-HBc) (if total anti-HBc is not available, record results from IgG test)*:	ng/mL
Positive (1)	
Negative $\binom{2}{2}$	

10	Ις	henatic	iron	index	available
IV.	15	nepatic	поп	muex	avallable

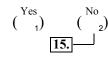


11. Hepatic iron index:

•	
μMo1/g/year	

D. HFE gene analysis

12. Does the patient have an abnormality in an iron overload screening test, a family history of iron overload or hemochromatosis, or histological iron of greater than 3+:



13. Date of blood draw for HFE gene analysis:

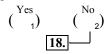
day	mon	year

14. Type of abnormality (WT = wild type; check only one):

None	(0
C282Y/H63D heterozygote mutation	(1)
C282Y/C282Y homozygote mutation	(2)
C282Y/WT heterozygote mutation	(3)
H63D/WT heterozygote mutation	(4)
H63D/H63D homozygote mutation	(5)

E. Ceruloplasmin

15. Is patient 40 years old or younger:



16. Date of blood draw for ceruloplasmin: (required only if patient is 40 years old or younger):



Repeat if date is greater than 10 years prior to screening.

17. Ceruloplasmin

•	
 mg/dL	
•	
 mg/dL	

a. Upper limit of normal: _

b. Lower limit of normal:		
	mg/dL	

F. Alpha-1 antitrypsin

18. Date of blood draw for alpha-1 antitrypsin (A1AT):

_	-	<u>_</u> ,
day	mon	year
	1 10	_

Repeat if date is greater than 10 years prior to screening.

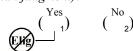
- 19. Alpha-1 antitrypsin (A1AT) _____ mg/dL ____
 - **a.** Upper limit of normal: _____ mg/dL ____
 - **b.** Lower limit of normal: $\underline{\hspace{1cm}}_{mg/dL} \underline{\hspace{1cm}}_{mg/dL}$
- **20.** A1AT phenotype (if unknown record as "m")
 - **a.** Pi Z heterozygote:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

b. Pi ZZ homozygote:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

21. A1AT deficiency (physician judgment):



G. Autoantibody studies

22. Date of blood draw for autoantibody tests:

		<u>=</u>
day	mon	year
Repeat if date is greater	r than 5	years prior to
screening.		

23. Antinuclear antibody (ANA):

Positive	(*1)
Negative	(2)
	24.

^{*}If results are given as units, record as "n," and key the actual result in the General Comments.

24.	Antismooth	muscle	antibody	(ASMA))
-----	------------	--------	----------	--------	---

Positive (*1)
Negative (25.

a. If positive, ASMA: 1/____ ___ ___

*If results are given as units, record as "n," and key the actual result in the General Comments.

25. Antimitochondrial antibody (AMA)*:

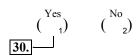
Positive (†1)
Negative (26)

a. If positive, AMA: 1/ ____ ___ ___

*Optional if patient under age 18, enter 'm''if not done.

†If results are given as units, record as "n," and key the actual result in the General Comments.

26. Is the patient 18 or older:



27. Lymphocytotoxic antibody (LCA)*:

Positive (1)
Negative (2)

a. If positive, LCA: 1/____ ____

28. Antibody to liver-kidney microsomal antigen (LKM1)*:

Positive (1)
Negative (2)

29. Rheumatoid factor (RF)*:

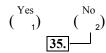
Positive (1)
Negative (2)

a. If positive, RF: ____ ___ ___

*Optional - record as "m" if test is not done

H. Immunoglobulin levels

30. Are immunoglobulin levels available:



31. Date of blood draw for immunoglobulin levels:

day	mon	year

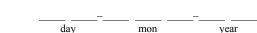
32. IgA: ______mg/dL _____

33. IgG: ______ ____ ____

34. IgM: ______ mg/dL

I. Other screening blood tests

35. Date of blood draw for thyroid stimulating hormone (TSH)*:



Repeat if date is greater than 5 years prior to screening. *Optional if patient under age 18, enter 'm' if not done.

36. Thyroid stimulating hormone:

•	
 μU/mL	

Patient ID:	 	

T	A .1		4	: C	mation
. I .	Aan	mistr	'arive	inior	manon

day

37.	Study Physician PIN:	 _
38.	Study Physician signature:	
39.	Clinical Coordinator PIN:	 _
40.	Clinical Coordinator signature:	
41.	Date form reviewed:	

mon

year

LT - Liver Tissue Banking

Purpose: To document collection of extra liver tissue and flash freeze procedures for liver specimen banking. **When**: Whenever more than 2 cm of liver tissue are obtained during a biopsy. If you have more than one pre-enrollment biopsy with flash frozen liver tissue available, contact the Data Coordinating Center. Only one LT form may be completed prior to enrollment in the Database. Use visit code s1, f024, f048, f096, f144, f192, or in followup, use the code for the followup visit that is currently open (check the patient's visit time window guide). If after enrollment and before the f024 window is open, use visit code "n". This form is expected whenever the Liver Biopsy Materials Documentation (SD) form says liver tissue was obtained for banking.

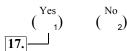
By whom: Clinical Coordinator.

Instructions: Liver biopsy tissue should be obtained by a needle core biopsy (as opposed to a wedge biopsy) using a 16 or greater gauge needle. Whenever more than 2 cm of tissue are obtained during biopsy, place a 1-2 mm segment of liver tissue into a 2.0 mL polypropylene cryovial with preprinted label attached. Flash freeze liver tissue immediately (within 5 minutes following biopsy) by placing labeled cryovial containing liver tissue into a portable liquid nitrogen container. Store the cyrovial locally in -70° C (or colder) freezer temporarily and batch ship cryovials on dry ice monthly to the NIDDK Biosample Repository located at McKesson Bioservices.

A. Center, patient and visit identification	11. Was the liver tissue obtained from a needle core biopsy (as opposed to a wedge bi-
1. Center code:	opsy): Yes $\begin{pmatrix} N_0 \\ 1 \end{pmatrix}$
2. Patient ID:	C. Cryovial label
3. Patient code:	12. Attach duplicate cryovial label:
4. Date form initiated:	
day mon year	-
5. Visit code (s1, n, or code for followup visit that is open):	_
6. Form & revision:	-
7. Study: NAFLD Database 1	
B. Liver biopsy	D. Flash freeze procedures
8. Date of biopsy:	13. Was tissue flash frozen within 5 minutes of biopsy by placing in portable liquid nitrogen container:
day mon year	Yes $\binom{\text{No}}{1}$ $\binom{\text{No}}{2}$
9. Was the liver tissue obtained using a 16-gauge or greater needle:	15.
$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$	2) 14. Explain what was done and why protocol was not followed:
10. Was liver tissue obtained via a second	
pass: $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	

Patient ID:		

15. Was tissue shipped on dry ice to the Biosample Repository on same day as biopsy:



16. Describe conditions of local storage prior to shipment to the Biosample Repository (e.g., temperature, date and time placed in freezer):

1	*	1	0	/

E. Administrative information

- **17.** Clinical Coordinator PIN: ____ ___
- 18. Clinical Coordinator signature:

MA - Modifiable Activity Questionnaire

Purpose: To obtain the patient's physical activity.

When: Visits s2, f048, f096, f144, and f192.

Administered by: Interview administered or self-administered, depending on the age of the patient. Parents may assist with completion, if needed. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 8-17.

Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-3. The patient should meet with the interviewer, be trained in completion of the form, and then should complete pages 2-3. If needed, the Clinical Coordinator may administer the interview to the patient. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B below.

A.	Center, patient, and	visit identification	B. Administrative information
1.	Center ID:		(To be completed by the Clinical Coordinator after survey is completed).
2.	Patient ID:		8. How was the questionnaire completed: Self-administered by patient/parent ()
3.	Patient code:		10.
4.	Date of visit (date pa	tient completed the form):	Interview in English (2) Interview with translator (3)
	-	month year	9. Who was the respondent (check all that apply) a. Patient: b. Patient's mother or female guardian:
5.	Visit code:		c. Patient's father or male guardian: d. Other, <i>specify</i> :
6.	Form & revision:	<u>m a 1</u>	
_	G. 1	WATER DOLLAR	10. Clinical Coordinator
7.	Study:	NAFLD Database 1	a. PIN:
			b. Signature:
			11. Date form reviewed:
			day month year

Affix Label Here
Patient ID:
Patient code:
Visit code:

Modifiable Activity Questionnaire

(Items 1-11 are reserved for clinic use.)

12.	How many times in the past 14 days have you done at least 20 minutes of exercise hard enough to make you
	breathe heavily and make your heart beat fast? (Hard exercise includes, for example, playing basketball,
	jogging, or fast bicycling; include time in physical education class)?

	Circle one
None	1
1 to 2 days	2
3 to 5 days	
6 to 8 days	
9 or more days	5

13. How many times in the past 14 days have you done at least 20 minutes of <u>light</u> exercise that <u>was not</u> enough to make you breathe heavily and make your heart beat fast? (Light exercise includes playing basketball, walking or slow bicycling; include time in physical education class)?

	Circle one
None	1
1 to 2 days	2
3 to 5 days	
6 to 8 days	4
9 or more days	5

14. During a normal week how many <u>hours a day</u> do you watch television and videos, or play computer or video games, or use the computer for other activities before or after school?

	Circle one
None	1
1 hour or less	2
2 to 3 hours	3
4 to 5 hours	4
6 or more hours	5

15. During the past 12 months, how many team or individual <u>sports</u> or activities did you participate in on a <u>competitive</u> level, such as varsity or junior varsity sports, intramurals, or out-or-school programs?

	Circle one
None	1
1 activity	2
2 activities	3
3 activities	4
4 or more activities	
What activities did you compete in?	

Affix Label Here
Patient ID:
Patient code:
Visit code:

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

16.			ST YEAR. Do not include time spent in school u participated in during the last year.
	 01. Aerobics 04. Basketball 07. Cheerleading 10. Garden/Yard Work 13. Ice Skating 16. Skateboarding 19. Softball 22. Tennis 25. Weight Training (Competitive) 	 () 02. Band/Drill Team () 05. Bicycling () 08. Dance Class () 11. Gymnastics () 14. Roller Skating () 17. Snow Skiing () 20. Street Hockey () 23. Volleyball () 26. Wrestling 	 () 03. Baseball () 06. Bowling () 09. Football () 12. Hiking () 15. Running and Exercise () 18. Soccer () 21. Swimming () 24. Water Skiing () 27. Others:
	2 2	ked above in the "Activity" box be activity and then estimate the an	pelow. nount of time spent in each activity.

Activity Code #	Activity	J A N	F E B	M A R	A P R	M A Y	J U N	J U L	A U G	S E P	O C T	N O V	D E C	Months per Year	Days per Week	Minutes per Day
															_	
															_	
															_	
															_	

17.	Loday	's date:	
	-		

MV - Missed or Incomplete Visit

Purpose: Record reason(s) for missed or incomplete visit.

When: At the close of a visit window for any missed followup visit or for any followup visit with specific forms not completed. Use visit code f024, f048, f096, f144, or f192.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in

missing forms) within the time window for the visit.

Δ	Center	patient.	and	visit	iden	tifica	tion
A.	Center,	pauent	anu	VISIL	iueii	unca	uoi

- **1.** Center ID: ____ __ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- 4. Date of visit:

_		_
day	mon	year

- **5.** Visit code: __f__ _____
- 7. Study: NAFLD Database 1

B. Reason for completion of this form

8. Was the entire visit missed:

$$\binom{\text{Yes}}{1} \qquad \binom{\text{No}}{2}$$

C. Missed visit information

- 9. Reason for missed visit (check all that apply)
 - **a.** Patient was ill:
 - **b.** Patient was temporarily away from area:
 - **c.** Patient refused to return:
 - to retain.
 - **d.** Patient has permanently moved from the area:
 - e. Unable to contact patient: (1)
 - **f.** Other (specify):

specify

- **10.** Steps taken to avoid missing the visit (check all that apply)
 - a. Telephoned patient: (
 - **b.** Mailed reminder card:
 - **c.** Other (specify):

specify

14.

D. Missed form information

Check form(s) not completed (check required forms that were missed)		
a. Food Questionnaire Documentation (BD):	(1)
b. Blood Processing for Plasma and Serum (BP):	(1)
c. Followup Medical History (HI):	(1)
d. Liver Imaging Studies Report (IR):	(1)
e. Symptoms of Liver Disease (Children) (LP):	(1)
f. Symptoms of Liver Disease (LQ):	(1)
g. Laboratory Results - Tests Done During Screening and Followup (LR):	(1)
h. Modifiable Activity Questionnaire (MA):	(1)
i. Physical Activity (PA):	(1)
j. Physical Examination (PE):	(1)
k. Focused Physical Examination (PF):	(1)
1. Pediatric Quality of Life: Parent of adolescent age 13-17 (PQ):	(1)
m. Pediatric Quality of Life: Parent of child age 8-12 (PR):	(1)
n. Pediatric Quality of Life: Parent of child age 5-7 (PS):	(1)
o. Pediatric Quality of Life: Parent of toddler (PT):	(1)
p. Pediatric Quality of Life: Child age 5-7 (PV):	(1)
q. Pediatric Quality of Life: Child age 8-12 (PW):	(1)
r. Pediatric Quality of Life: Adolescent age 13-17 (PY):	(1)
s. MOS 36-Item Short-form Health Survey (QF):	(1)
t. Other (specify):	(1)
specify		

12.	B 0 / 1 1 1		
	Reason form(s) not completed (check all that apply)		
	a. Patient was ill:	(1)
	b. Patient refused procedure:	(1)
	c. Parent refused procedure:	(1)
	d. Procedure forgotten:	(1)
	e. Other (specify):	(1)
	specify		
13.	Attempts made to complete form(s) (checapply)	kalli	hat
	a. Attempted to reschedule procedure:	(1)
	b. Attempted to collect interview data by phone from patient/family:	(1)
	c. Attempted to gain patient/parent cooperation:	(1)
	d. Other (specify):	(1)
	specify		
E. A	dministrative information		
14.	Clinical Coordinator PIN:		
15.	Clinical Coordinator signature:		
	Date form reviewed:		
16.			

E.

Purpose: To obtain the patient's physical activity.

When: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered, but Clinical Coordinator must be available at visits to answer questions and review completed forms.

Respondent: Patient, 18 years of age or older, without help from spouse or family.

Instructions: The Clinical Coordinator should complete section A below and attach a label to each of pages 2-4.

Screening: The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-4. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should complete section B below. Followup: Pages 2-4 should be mailed to the patient 2 weeks prior to the scheduled study visit with instructions to complete the form at home and to bring the completed form to the next study visit. When the patient returns for the visit, the Clinical Coordinator should review the form for completeness and obtain responses for missing items during the visit. If the patient did not bring a completed form to the visit, the patient should complete the form at the visit. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should complete section B. Item 4 should be completed with the date the patient wrote in item 39. If the patient did not write in a date, use the date of the study visit for the visit date.

. Ce	enter, patient, and visi	it identification	B. Administrative information (To be completed by Clinical Coordinator after	
1.	Center ID:		survey is completed.)	
2.	Patient ID:		8. Clinical Coordinator a. PIN:	
3.	Patient code:		b . Signature:	
4.	Date of visit (date pa	tient completed the form):		_
		mon year	9. Date form reviewed:	
5.	Visit code:		day mon year	
6.	Form & revision:	<u>p</u> <u>a</u> <u>1</u>		
7	Study.	NAFLD Database 1		

Affix label here				
Patient ID:				
Patient code:				
Visit code:				

PA - Physical Activity

Instructions: This survey asks for your views about your physical activity. (*Items 1-9 are reserved for clinical center use*).

C. Non-Recreational Activity (Work Related)

The following questions are about your non-recreational activity. Non-recreational activity is what you consider your main day to day activity, at work or at home, whether you get paid or not.

10.	Circle one Level of activity that best describes your usual non-recreational activity.					
	Vigorous or strenuous activity:					
	Moderate activity:					
	(requires moderate-paced walking on a flat surface, heavy one-arm work or moderate two-arm work, such as picking, sweeping, lifting light objects, or heavy housework)					
	Light activity:					
11.	On average, how many hours per day do you spend at this level of activity?					
	Hours					
12.	On average, how many hours per day do you spend sitting down?					
	Hours					

Affix label here
Patient ID:
Patient code:
Visit code:

D. Recreational Activity (Non-Work Related)

The following questions are about the recreational activities you spend at least 15 minutes doing each week. You should count walking or biking to work and any other activities outside of work. Next to each activity that you participate in, write in how many total hours or minutes you do that activity on an average week. Mark the places for hours and minutes only for the activities you participate in.

For each activity that you engage in for at least 15 minutes per week, please circle the activity and write the number of hours or minutes that you do that activity per week.				
13.	Swimming	Hours:	Minutes:	
14.	Jogging		Minutes:	
15.	Running	Hours:	Minutes:	
16.	Brisk walking	Hours:	Minutes:	
17.	Bicycling on hills	Hours:	Minutes:	
18.	Bicycling on flat surfaces	Hours:	Minutes:	
19.	Hiking or climbing	Hours:	Minutes:	
20.	Yard work / Gardening	Hours:	Minutes:	
21.	Aerobics	Hours:	Minutes:	
22.	Dancing	Hours:	Minutes:	
23.	Calisthenics (exercises without machines)	Hours:	Minutes:	
24.	Weight lifting, using weight machines, or heavy lifting	Hours:	Minutes:	
25.	Treadmill or Stairmaster	Hours:	Minutes:	
26.	Chopping wood	Hours:	Minutes:	

Affix label here			
Patient ID:	. — ¦		
Patient code:			
Visit code:			

For each activity that you engage in for at least 15 minutes per week, please circle the activity and write the number of hours or minutes that you do that activity per week.					
27.	Painting / Woodworking	Hours:	Minutes:		
28.	Housecleaning		Minutes:		
29.	Golfing		Minutes:		
30.	Singles tennis, racquetball, or other court sports		Minutes:		
31.	Doubles tennis, racquetball or other court sports	Hours:	Minutes:		
32.	Basketball	Hours:	Minutes:		
33.	Football, soccer, or other field sports		Minutes:		
34.	Skiing	Hours:	Minutes:		
35.	Bowling	Hours:	Minutes:		
Others (write in the name of activity):					
36.	Name of activity	Hours:	Minutes:		
37.	Name of activity	Hours:	Minutes:		
38.	Name of activity	Hours:	Minutes:		
39.	Today's date:				

Thank you for completing this survey. Please bring this completed survey with you to your scheduled NASH CRN study visit.

PE - Physical Examination

Purpose: Record detailed physical exam findings. **When**: Visits s1, f048, f096, f144, and f192.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurements are found in NAFLD Database SOP, Part I. In brief: Height, weight, waist and hips all should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other. Skin fold and mid-upper arm circumference should be measured on the right arm with the elbow extended and the arm relaxed. Repeat skin fold measurements until you have two measurements within 10 mm of each other. Repeat mid-upper arm circumference measurements until you have two within 1.5 in (3.8 cm) of each other.

A. Center, patient, and vis	sit identificat	tion	9. Weight (shoes off)
1. Center ID:			a. Weight, 1st measurement:
2. Patient ID:			b. Weight, 2nd measurement:
3. Patient code:			
4. Visit date:			Pounds (Kilograms (
day mon year 10. Waist (standing, at midpo of iliac crest and lowes repeat waist measurement)		10. Waist (standing, at midpoint between highest poi of iliac crest and lowest part of costal margin repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each othe	
6. Form & revision:	<u>p</u>	e2_	a. Circumference, 1st measurement:
7. Study:	NAFLD Da	atabase <u>1</u>	waist circumference b. Circumference, 2nd measurement:
B. Measurements			waist circumference
8. Height (shoes off)			c. Units:
a. 1st measurement:		•	Inches (Centimeters (
b. 2nd measurement:		_ •	11. Hip (standing, at fullest part of the hips; repeat h measurements until you have two measuremen within 4 in (10.2 cm) of each other)
c. Units: Inches		(1)	a. Circumference, 1st measurement:
Centimeters		$\begin{pmatrix} 1 \\ 2 \end{pmatrix}$	
		, -	hip circumference
			b. Circumference, 2nd measurement:
			hip circumference
			c. Units:
			Inches (
			Centimeters

12. Triceps (right arm, with elbow extended and arm		18. Acanthosis nigricans (check on	ly one):
relaxed; repeat skin fold m have two within 10 mm o	of each other; repeat	Absent (not detectable on close	e inspection) $\begin{pmatrix} 0 \end{pmatrix}$
mid-upper arm circumferen you have two within 1.5 in ((3.8 cm) of each other)	Present (clearly present on clo	se
a. Skin fold, 1st measurement:		inspection, not visible to casua extent not measurable)	$\begin{pmatrix} 1 \end{pmatrix}$
b. Skin fold, 2nd measurem	mm — —	Mild (limited to base of skull, rextending to lateral margins of < 3 inches in breadth)	not rneck, (₂)
		Moderate (extending to lateral	margins
c. Mid-upper arm circumfer		of neck, 3-6 inches in breadth, from patient's front)	not visible $\binom{3}{3}$
measurement:	arm circumference	Severe (extending anteriorly, > breadth, visible from front)	6 inches in (4)
d. Mid-upper arm circumfe measurement:	rence, 2nd	10 04 1: 1 1: (1.1	11 (1 (1)
measurement.	arm circumference	19. Other skin abnormality <i>(check)</i>	11.07
e. Units for arm circumfere		a. Jaundice:	(1)
Inches	(₁)	b. Palmar erythema:	(1)
Centimeters	$\begin{pmatrix} 1 \\ 2 \end{pmatrix}$	c. Spider angiomata:	(1)
	(2)	d. Other (specify):	(1)
13. Temperature (Oral or other, as appropri	iate for age)		, , ,
(Oral or other, as appropri	idic for age,	e. None of the above:	()
a. Degrees:		e. None of the above.	(1)
b. Scale:		20. Head, eyes, ears, nose, throat:	
Fahrenheit	()	Normal	(1)
Centigrade	$\begin{pmatrix} & & 1 \\ & & 2 \end{pmatrix}$		22.
-	(2)	Abnormal	(2)
14. Blood pressure		21. Abnormality of the head, eyes,	nose,
a. Systolic:		throat (check all that apply)	,
	mm ig	a. Jaundice:	(1)
b. Diastolic:	mmHg	b. Other (specify):	(1)
15. Resting radial pulse:	beats/minute	specify	
16. Respiratory rate:		22. Neck:	
Tot Itopiuuoij iute.	breaths/minute	Normal	()
C. Examination findings		1,011101	23
C. Dammadon munigs		Abnormal	(2)
17. Skin:			
Normal	(1)	specify abnorma	llity
Abnormal	20.		
Autiorillai	(2)		

23. Lymphatic:

Normal

specify abnormality

24. Chest and lungs:

Abnormal

Normal

Abnormal

25. Heart:

Normal

Abnormal

specify abnormality

specify

26. Abdomen:

Normal

Abnormal

27. Abdomen abnormality *(check all that apply)*

a. Ascites:

b. Obese:

c. Other (specify):

specify

28. Liver and spleen:

Normal

Abnormal

29. Abnormality of liver or spleen (check all that ap-

a. Hepatomegaly: (if checked, span from right midclavicular

b. Splenomegaly:

c. Other (specify):

specify

30. Extremities:

Not performed

Normal Abnormal

31. Abnormality of the extremities *(check all that apply)*

a. Contractures:

b. Muscle wasting:

c. Palmar erythema:

d. Pedal edema:

e. Other (specify):

32. Genitourinary/pelvis: Not performed

specify

Abnormal

Normal

specify

33. Nervous system:

Not performed

Abnormal

Normal

- **34.** Abnormality of the nervous system *(check all that apply):*
 - **a.** Mental status abnormal: (1) **b.** Asterixis: (1)
 - c. Other (specify):

specify

D. Tanner Staging

35. Is Tanner staging required for this participant (*Note: Required at screening visit if participant is 17 years old or younger.) (check only one):*

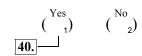
Yes, participant has not reached full sexual maturity or is 17 years old or younger:

No, participant is 18 years old or older

No, participant had reached full sexual maturity (Tanner stage 5 on all parameters at screening or for 2 consecutive visits)



36. Is the patient female:



Male Tanner Staging

37. Genital stage:

1-5

38. Testicular volume (smallest of right and left):



39. Pubic hair stage:



Female Tanner Staging

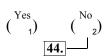
40. Breast stage:

1-5

41. Pubic hair stage:

1-5

42. Has menarche occurred:



43. What was the participant's age at menarche:

age in years

- E. Administrative information
- **44.** Study Physician PIN:
- **45.** Study Physician signature:
- **46.** Clinical Coordinator PIN:
- **47.** Clinical Coordinator signature:
- 48. Date form reviewed:

 day mon year

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.

When: Visit f024.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurement are found in the NAFLD Database SOP Part I. In brief: height, weight, waist and hips should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

A. Center, patient, and visit identification		9. Weight (shoes off)		
1. Center ID:		a. 1st measurement:	•	
2. Patient ID:		b. 2nd measurement:		
3. Patient code:		c. Units:		
4. Visit date:		Pounds Kilograms	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	
day 5. Visit code:	mon year _f 0 2 4	10. Waist (standing, at midpoint betwo filiac crest and lowest point of repeat waist measurements untimeasurements within 4 in (10.2 c	of costal margin; til you have two	
6. Form & revision:	_pf2_	a. 1st measurement:	•	
7. Study:	NAFLD Database 1	b. 2nd measurement:	•	
B. Measurements		c. Units:		
8. Height (shoes off) a. 1st measurement:		Inches Centimeters	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	
b. 2nd measurement:		11. Hip (standing, at fullest part of waist measurements until you haments within 4 in (10.2 cm) of each	ave two measure-	
		a. 1st measurement:		
c. Units: Inches Centimeters	$\begin{pmatrix} & & 1 \\ & & 1 \end{pmatrix}$	b. 2nd measurement:	• — • — —	
		c. Units: Inches	(1)	
		Centimeters	$\begin{pmatrix} 1 \\ 2 \end{pmatrix}$	

12. Temperature (oral or other as ap	ppropriate for age	D. Administrative information						
a. Degrees:								
b. Scale: Fahrenheit: Centigrade:		18. Study Physician signature: 1) 10 11 11 12						
13. Blood pressure		19. Clinical Coordinator PIN:						
a. Systolic:	mmHg	20. Clinical Coordinator signature:						
b. Diastolic:	mmHg							
14. Resting radial pulse:	beats/minute	21. Date form reviewed:						
15. Respiratory rate:	breaths/minus	_						
C. Focused liver signs								
16. Abnormality (check all that app	oly)							
a. Ascites:	(1	1)						
b. Asterixis:	(1	1)						
c. Contractures:	(1	1)						
d. Hepatic encephalopathy:	(1	1)						
e. Hepatocellular carcinoma:	(1	1)						
f. Hepatomegaly:	(1	1)						
If Yes, span from right midcl	avicular line:							
	em •	_						
g. Hepatopulmonary syndrome:		1)						
h. Hepatorenal syndrome:	(1	1)						
i. Jaundice:	(1	1)						
j. Muscle wasting:	(1	1)						
k. Palmar erythema:	(1	1)						
I. Pedal edema:	(1	1)						
m. Portal hypertension:	(1	1)						
n. Spider angiomata:	(1	1)						
o. Splenomegaly:	(1	1)						
p. Other, (specify):	(1	1)						
q. None of the above	(1	<u>,)</u>						

PQ – Pediatric Quality of Life: Parent Report for Teens (Age 13-17)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of teens, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #10, Instructions for Pediatric Quality of Life (Forms PQ, PR, PS, and PT) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be re-attached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	enter, patient, and visi	t identification		lministrative information To be completed by Clinical Coordinator afte	er					
1.	Center ID:		survey is completed.)							
2.	Patient ID:		8.	How was the Pediatric Quality of Life questionnaire completed:						
3.	Patient code:			Calcadorinistant in English	,	`				
4.	Date form completed			Self-administered in English Self-administered in Spanish Interview in English Interview in Spanish	(1) 2) 3)				
	day	mon year		Interview in Spanish	(4)				
5.	Visit code:		9.	Clinical Coordinator a. PIN: b. Signature:						
6.	Form & revision:	<u> </u>		b. Signature.						
7.	Study:	NAFLD Database 1	10.	Date form reviewed:						
				day mon	year					

PQ - Pediatric Quality of Life:
Parent Report for Teens (Age 13-17)

Affix label here						
Patient ID:						
Patient code:						
Visit code:						

In the past **ONE month**, how much of a **problem** has your teen had with...

PHYSICAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in sports activity or exercise:	0	1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores around the house:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:	0	1	2	3	4

EMOTIONAL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

Soci	IAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	Getting along with other teens:	0	1	2	3	4
25.	Other teens not wanting to be his or her friend:	0	1	2	3	4
26.	Getting teased by other teens:	0	1	2	3	4
27.	Not able to do things that other teens his or her age can do:	0	1	2	3	4
28.	Keeping up with other teens:	0	1	2	3	4

PedsQl 4.0 - Parent (13-17)

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Patient ID:
Patient code:
Visit code:

SCH	OOL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	Keeping up with schoolwork:	0	1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

A

PR – Pediatric Quality of Life: Parent Report for Children (Age 8-12)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of child, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #10, Instructions for Pediatric Quality of Life (Forms PQ, PR, PS, and PT) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be re-attached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

. С	enter, patient, and visit	t identification	B. Administrative information	Cton	
1.	Center ID:		(To be completed by Clinical Coordinator at survey is completed.)	ier	
2.	Patient ID:		8. How was the Pediatric Quality of Life questionnaire completed:		
3.	Patient code:		Self-administered in English	(1)
4.	Date form completed:		Self-administered in Spanish Interview in English	(2) 3)
	day	mon year	Interview in Spanish	(4)
5.	Visit code:		9. Clinical Coordinator a. PIN: b. Signature:		
6.	Form & revision:	<u> </u>	1		
7.	Study:	NAFLD Database	10. Date form reviewed:		
			day mon	year	

Affix label here	
Patient ID:	_
Patient code:	
Visit code:	_

PR - Pediatric Quality of Life: Parent Report for Children (Age 8-12)

In the past **ONE month**, how much of a **problem** has your child had with...

PHYSICAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in sports activity or exercise:	0	1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores around the house:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:	0	1	2	3	4

ЕМО	TIONAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

Soc	IAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	Getting along with other children:	0	1	2	3	4
25.	Other kids not wanting to be his or her friend:	0	1	2	3	4
26.	Getting teased by other children:	0	1	2	3	4
27.	Not able to do things that other children his or her age can do:	0	1	2	3	4
28.	Keeping up when playing with other children:	0	1	2	3	4

PedsQI 4.0 - Parent (8-12)

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Affix label here
Patient ID:
Patient code:
Visit code:

SCH	OOL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	Keeping up with schoolwork:	0	1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

NAFLD Database

3 of 3

A

PS – Pediatric Quality of Life: Parent Report for Young Children (Age 5-7)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of child, age 5-7.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #10, Instructions for Pediatric Quality of Life (Forms PQ, PR, PS, and PT) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be re-attached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

. С	enter, patient, and visit	t identification			lministrative information	ton	
1.	Center ID:			,	To be completed by Clinical Coordinator aft urvey is completed.)	er	
2.	Patient ID:			8.	How was the Pediatric Quality of Life questionnaire completed:		
3.	Patient code:				Self-administered in English	(1)
4.	Date form completed:				Self-administered in Spanish Interview in English	(₂) ₃)
	day	mon	year		Interview in Spanish	(4)
5.	Visit code:			9.	Clinical Coordinator a. PIN: b. Signature:		
6.	Form & revision:	<u> </u>	<u>s</u> <u>1</u>		b. Signature.		
7.	Study:	NAFLD Da	atabase <u>1</u>	10.	Date form reviewed:		
					a	year	

Affix i	label here
Patient ID:	
Patient code:	
Visit code:	

PS - Pediatric Quality of Life: Parent Report for Young Children (Age 5-7)

In the past **ONE month**, how much of a **problem** has your child had with...

PHYSICAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in sports activity or exercise:	0	1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores, like picking up his or her toys:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:	0	1	2	3	4

ЕМО	EMOTIONAL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

Soc	SOCIAL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
24.	Getting along with other children:	0	1	2	3	4
25.	Other kids not wanting to be his or her friend:	0	1	2	3	4
26.	Getting teased by other children:	0	1	2	3	4
27.	Not able to do things that other children his or her age can do:	0	1	2	3	4
28.	Keeping up when playing with other children:	0	1	2	3	4

PedsQI 4.0 - Parent (5-7)

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Affix label here
Patient ID:
Patient code:
Visit code:

SCH	SCHOOL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	Keeping up with school activities:	0	1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PT – Pediatric Quality of Life: Parent Report for Toddlers (Age 2-4)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of child, age 2-4.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #10, Instructions for Pediatric Quality of Life (Forms PQ, PR, PS, and PT) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be re-attached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

. Center, patient, and visit identification				B. Administrative information (To be completed by Clinical Coordinator after					
1.	Center ID:				o be completed by Clinical Coordinator ap urvey is completed.)	ier			
2.	Patient ID:			8.	How was the Pediatric Quality of Life questionnaire completed:				
3.	Patient code:				Self-administered in English	(1)		
4.	Date form completed:				Self-administered in Spanish Interview in English	(2) 3)		
	day	mon -	year		Interview in Spanish	(4)		
5.	Visit code:			9.	Clinical Coordinator a. PIN: b. Signature:				
6.	Form & revision:	<u> </u>	1_		b. Digitato.				
7.	Study:	NAFLD Data	base <u>1</u>	10.	Date form reviewed:				
					day mon	vear			

Affix l	abel here
Patient ID:	
Patient code:	
Visit code:	

PT - Pediatric Quality of Life: Parent Report for Toddlers (Age 2-4)

In the past ONE month, how much of a problem has your child had with...

PHYSICAL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
11. Walking:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in active play or exercise:	0	1	2	3	4
14. Lifting something heavy:		1	2	3	4
15. Bathing:	0	1	2	3	4
16. Helping to pick up his or her toys:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:		1	2	3	4

EMOTIONAL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying:	0	1	2	3	4

Soc	SOCIAL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
24.	Playing with other children:	0	1	2	3	4
25.	Other kids not wanting to play with him/her:	0	1	2	3	4
26.	Getting teased by other children:	0	1	2	3	4
27.	Not able to do things that other children his or her age can do:	0	1	2	3	4
28.	Keeping up when playing with other children:	0	1	2	3	4

PedsQI 4.0 - Parent (2-4)

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Affix label here
Patient ID:
Patient code:
Visit code:
L

*Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
29.	Doing the same school activities as peers:	0	1	2	3	4
30.	Missing school/daycare because of not feeling well:	0	1	2	3	4
31.	Missing school/daycare to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PV – Pediatric Quality of Life: Young Child Report (Age 5-7)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192. **Administered by**: Clinical Coordinator.

Respondent: Patient, age 5-7.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-4. The Clinical Coordinator should interview the child following the instructions on page 2 and using Flash Card #11, Template for Pediatric Quality of Life (Form PV). Page 1 should be re-attached to pages 2-4 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Co	enter, patient, and visi	it identification	B. Administrative information (To be completed by Clinical Coordinator after	
1.	Center ID:		survey is completed.)	
2.	Patient ID:		8. How was the Pediatric Quality of Life questionnaire completed:	
3.	Patient code:		Interview in English ()	.)
4.	Date form completed	l:	Interview with translator (2)	`
	day -	mon year	9. Clinical Coordinator a. PIN:	_
5.	Visit code:		b . Signature:	
6.	Form & revision:	<u> </u>	10. Date form reviewed:	_
7.	Study:	NAFLD Database 1	<u>-</u>	
			day mon year	_

	Affix label here				
Patient ID:					
Patient code:					
Visit code:					

PV - Pediatric Quality of Life: Young Child Report (Age 5-7)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show child the template and point to the responses as you read.

If it is not at all a problem for you, point to the smiling face

If it is sometimes a problem for you, point to the middle face

If it is a problem for you a lot, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
It is hard for you to snap your fingers	>	?	@

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

Affix label he	ere
Patient ID:	
Patient code:	
Visit code:	

PV - Pediatric Quality of Life: Young Child Report (Age 5-7)

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHY	SICAL FUNCTIONING (problems with)	Not at all	Sometimes	A lot
11.	It is hard for you to walk:	0	2	4
12.	It is hard for you to run:	0	2	4
13.	It is hard for you to play sports or exercise:	0	2	4
14.	It is hard for you to pick up big things:	0	2	4
15.	It is hard for you to take a bath or shower:	0	2	4
16.	It is hard for you to do chores (like pick up your toys):	0	2	4
17.	Do you have hurts or aches (Where?):	0	2	4
18.	Do you ever feel too tired to play:	0	2	4

ABOUT MY FEELINGS (problems with)		Not at all	Sometimes	A lot
19.	Do you feel scared:	0	2	4
20.	Do you feel sad:	0	2	4
21.	Do you feel mad:	0	2	4
22.	Do you have trouble sleeping:	0	2	4
23.	Do you worry about what will happen to you:	0	2	4

HOW I GET ALONG WITH OTHERS (problems with)		Not at all	Sometimes	A lot
24.	Is it hard for you to get along with other kids:	0	2	4
25.	Do other kids say they do not want to play with you:	0	2	4
26.	Do other kids tease you:	0	2	4
27.	Can other kids do things that you cannot do:	0	2	4
28.	It is hard for you to keep up when you play with other kids:	0	2	4

PedsQI 4.0 - (5-7)

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Affix label here
Pt ID:
Pt code:
Visit code:
Ĺ

ABO	UT SCHOOL (problems with)	Not at all	Sometimes	A lot
29.	It is hard for you to pay attention in school:	0	2	4
30.	Do you forget things:	0	2	4
31.	Is it hard to keep up with schoolwork:	0	2	4
32.	Do you miss school because of not feeling good:	0	2	4
33.	Do you miss school because you have to go to the doctor's or hospital:	0	2	4

Thank you for completing this questionnaire.

A

PW – Pediatric Quality of Life: Child Report (Age 8-12)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #9, Instructions for Pediatric Quality of Life (Forms PW and PY) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

. С	enter, patient, and visi	t identification			lministrative information	efton	
1.	Center ID:				To be completed by Clinical Coordinator a crvey is completed.)	jier	
2.	Patient ID:			8.	How was the Pediatric Quality of Life questionnaire completed:		
3.	Patient code:		<u> </u>		Self-administered in English	(1)
4.	Date form completed:				Self-administered in Spanish Interview in English Interview in Spanish	(₂) ₃)
	day	mon	year		interview in Spanish	(4)
5.	Visit code:			9.	Clinical Coordinator a. PIN: b. Signature:		
6.	Form & revision:	_pw	1		b. Signature.		
7.	Study:	NAFLD Dat	abase <u>1</u>	10.	Date form reviewed:		
					day mon	year	

Affix labe	l here
Patient ID:	
Patient code:	
Visit code:	

PW - Pediatric Quality of Life: Child Report (Age 8-12)

In the past **ONE month**, how much of a **problem** has this been for you...

ABOUT MY HEALTH AND ACTIVITIES (problems with)		Almost Never	Some- times	Often	Almost Always
11. It is hard for me to walk more than one block:	0	1	2	3	4
12. It is hard for me to run:	0	1	2	3	4
13. It is hard for me to do sports activity or exercise:	0	1	2	3	4
14. It is hard for me to lift something heavy:	0	1	2	3	4
15. It is hard for me to take a bath or shower by myself:	0	1	2	3	4
16. It is hard for me to do chores around the house:	0	1	2	3	4
17. I hurt or ache:	0	1	2	3	4
18. I have low energy:	0	1	2	3	4

ABOUT MY FEELINGS (problems with)		Almost Never	Some- times	Often	Almost Always
19. I feel afraid or scared:	0	1	2	3	4
20. I feel sad or blue:	0	1	2	3	4
21. I feel angry:	0	1	2	3	4
22. I have trouble sleeping:	0	1	2	3	4
23. I worry about what will happen to me:	0	1	2	3	4

HOW I GET ALONG WITH OTHERS (problems with)			Almost Never	Some- times	Often	Almost Always
24. I have trouble getting along with other kids:		0	1	2	3	4
25.	25. Other kids do not want to be my friend:		1	2	3	4
26.	26. Other kids tease me:		1	2	3	4
27.	27. I cannot do things that other kids my age can do:		1	2	3	4
28.	It is hard to keep up when I play with other kids:	0	1	2	3	4

PedsQI 4.0 - (8-12)

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D. C. LID
Patient ID:
Patient code:
Visit code:

ABOUT SCHOOL (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29. It is hard to pay attention in class:		1	2	3	4
30. I forget things:		1	2	3	4
31. I have trouble keeping up with my schoolwork:		1	2	3	4
32. I miss school because of not feeling well:		1	2	3	4
33. I miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PY – Pediatric Quality of Life: Teen Report (Age 13-17)

Purpose: To obtain the patient's quality of life. **When**: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #9, Instructions for Pediatric Quality of Life (Forms PY and PW) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	enter, patient, and visi	t identification		B. Administrative information (To be completed by Clinical Coordinator after survey is completed.)						
1.	Center ID:		,							
2.	Patient ID:		8.	How was the Pediatric Quality of Life questionnaire completed:						
3.	Patient code:			Calcadaniaistandia Fastish		`				
4.	Date form completed			Self-administered in English Self-administered in Spanish Interview in English Interview in Spanish	(1) 2) 3)				
	day	mon y	year	interview in Spanish	(4)				
5.	Visit code:		9.	Clinical Coordinator a. PIN: b. Signature:						
6.	Form & revision:	<u> </u>	_1_	b. Signature.						
7.	Study:	NAFLD Datab	pase <u>1</u>	Date form reviewed:		_				
				day mon	year					

PY	- Pediatric Quality of Life:
	Adolescent (Age 13-17)

Affix i	label here
Patient ID:	
Patient code:	
Visit code:	

In the past **ONE month**, how much of a **problem** has this been for you...

ABOUT MY HEALTH AND ACTIVITIES (problems with)			Almost Never	Some- times	Often	Almost Always
11.	11. It is hard for me to walk more than one block:		1	2	3	4
12.	It is hard for me to run:	0	1	2	3	4
13.	13. It is hard for me to do sports activity or exercise:		1	2	3	4
14.	14. It is hard for me to lift something heavy:		1	2	3	4
15.	15. It is hard for me to take a bath or shower by myself:		1	2	3	4
16.	16. It is hard for me to do chores around the house:		1	2	3	4
17. I hurt or ache:		0	1	2	3	4
18.	I have low energy:	0	1	2	3	4

ABOUT MY FEELINGS (problems with)	Never	Almost Never	Some- times	Often	Almost Always
19. I feel afraid or scared:		1	2	3	4
20. I feel sad or blue:		1	2	3	4
21. I feel angry:		1	2	3	4
22. I have trouble sleeping:		1	2	3	4
23. I worry about what will happen to me:	0	1	2	3	4

HOW I GET ALONG WITH OTHERS (problems with)			Almost Never	Some- times	Often	Almost Always
24. I have trouble getting along with other teens:		0	1	2	3	4
25.	25. Other teens do not want to be my friend:		1	2	3	4
26.	26. Other teens tease me:		1	2	3	4
27.	27. I cannot do things that other teens my age can do:		1	2	3	4
28.	It is hard to keep up with my peers:	0	1	2	3	4

PedsQl 4.0 - (13-17)

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Affix label here					
Patient ID:					
Patient code:					
Visit code:					

ABOUT SCHOOL (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29. It is hard to pay attention in class:		1	2	3	4
30. I forget things:		1	2	3	4
31. I have trouble keeping up with my schoolwork:		1	2	3	4
32. I miss school because of not feeling well:		1	2	3	4
33. I miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

A

QF – MOS 36-Item Short-Form Health Survey

Purpose: To obtain the patient's views of his/her health.

When: Visits s2, f048, f096, f144, and f192.

Administered by: Self-administered, but Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, 18 years or age or older, without help from spouse or family.

Instructions: The Clinical Coordinator should complete section A below and attach a label to each of pages 2-7.

Screening: The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-7. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-7 and the Clinical Coordinator should complete section B below. Followup: Pages 2-7 should be mailed to the patient 2 weeks prior to the scheduled study visit with instructions to complete the form at home and to bring the completed form to the next study visit. When the patient returns for the visit, the Clinical Coordinator should review the form for completeness and obtain responses for missing items during the visit. If the patient did not bring a completed form to the visit, the patient should complete the form at the visit. Page 1 should be attached to pages 2-7 and the Clinical Coordinator should complete section B below. Fill in item 4 with the date the patient wrote in item 21. If the patient did not write in a date, use the date of the study visit for the visit date.

. Ce	nter, patient, and v	isit identification	B. Administrative information (To be completed by clinical center staff after survey)
1.	Center ID:		is completed.)
2.	Patient ID:		8. Clinical Coordinator a. PIN:
3.	Patient code:		b . Signature:
4.	Date of visit (date	patient completed the form):	
	day	mon year	9. Date form reviewed:
5.	Visit code:		day mon year
6.	Form & revision:	<u>q</u> <u>f</u> <u>1</u>	
7	Study	NAFID DATABASE 1	

Affix label here	
Patient ID:	į
Patient code:	
Visit code:	

QF - MOS 36-Item Short-Form Health Survey

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

(Items 1-9 are reserved for clinical center use.)

10. In general, would you say your health is:

C		Circle one
	Excellent	1
	Very good	2

11. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	I
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

Affix label here					
Patient ID:					
Patient code:					
Visit code:	——				

12. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Circle		Circle one	
	Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports:	1	2	3
b.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:	1	2	3
c.	Lifting or carrying groceries:	1	2	3
d.	Climbing several flights of stairs:	1	2	3
e.	Climbing one flight of stairs:	1	2	3
f.	Bending, kneeling, or stooping:	1	2	3
g.	Walking more than a mile:	1	2	3
h.	Walking several blocks:	1	2	3
i.	Walking one block:	1	2	3
j.	Bathing or dressing yourself:	1	2	3

13. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		Circle one	
		Yes	No
a.	Cut down on the amount of time you spent on work or other activities:	1	2
b.	Accomplished less than you would like:	1	2
c.	Were limited in the kind of work or other activities:	1	2
d.	Had difficulty performing the work or activities (for example, it took extra effort):	1	2

Affix label here				
Patient ID:				
Patient code:				
Visit code:				

14. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		Circle one	
		Yes	No
a.	Cut down on the amount of time you spent on work or other activities:	1	2
b.	Accomplished less than you would like:	1	2
c.	Didn't do work or other activities as carefully as usual:	1	2

15. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

	Circle one
	Not at all
	Slightly
	Moderately
	Quite a bit
	Extremely
16.	How much bodily pain have you had during the past 4 weeks?
	None
	Very mild
	Mild
	Moderate
	Severe
	Very severe

Affix label here	
Patient ID:	_
Patient code:	_
Visit code:	-

17. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

	Circle one
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

18. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

		Circle one					
		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of pep?	1	2	3	4	5	6
b.	Have you been a very nervous person?	1	2	3	4	5	6
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d.	Have you felt calm and peaceful?	1	2	3	4	5	6
e.	Did you have a lot of energy?	1	2	3	4	5	6
f.	Have you felt downhearted and blue?	1	2	3	4	5	6
g.	Did you feel worn out?	1	2	3	4	5	6
h.	Have you been a happy person?	1	2	3	4	5	6
i.	Did you feel tired?	1	2	3	4	5	6

Affix label here
Patient ID:
Patient code:
Visit code:

19. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

	Circle one
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

20. How TRUE or FALSE is *each* of the following statements for you.

		Circle one					
		Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
a.	I seem to get sick a little easier than other people	1	2	3	4	5	
b.	I am as healthy as anybody I know	1	2	3	4	5	
c.	I expect my health to get worse	1	2	3	4	5	
d.	My health is excellent	1	2	3	4	5	

21.	Today's date:	

Thank you for completing this survey. Please bring this completed survey with you to your scheduled NASH CRN study visit.

RC - Rescreen in Database

NAFLD Database

Purpose: To rescreen a patient who was previously found to be ineligible for the NAFLD Database due to a temporary ineligibility. This form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 120-day screening window is reckoned from). The original RG form completed for the patient must remain in the data system. New screening phase tube and questionnaire labels will be available for printing upon keying this form.

When: Visit code s1.

Administered by: Clinical Coordinator.

Respondent: None.

Instructions: Complete this form for a patient who was previously found to be ineligible for the NAFLD Database due to a temporary ineligibility and who now wants to rescreen for the NAFLD Database. In general, the patient must complete all Database screening data collection anew and all previously keyed Database screening forms should be deleted from the data system except the RG and possibly the BC and CG forms. Update sections B, C, D, and G of the RG form and update the keyed record (you cannot delete the RG form). If blood was collected successfully for the Genetics Repository, a new sample does not need to be collected and the previously completed BC and CG forms may remain unchanged in the data system. Plasma and serum must be collected anew. If the same liver biopsy is being used to satisfy eligibility now and slides were sent to the DCC, additional slides do not need to be sent. The SD/SE/SF, HE/HF/HG, and LT forms should be updated or completed anew as appropriate, transcribing the slide numbers and liver tissue vial number as needed.

A. Center, patient, and	visit identification	C. Administrative inform	mation	
1. Center ID:		9. Clinical Coordinator	PIN:	
2. Patient ID:		10. Clinical Coordinator	signature:	
3. Patient code:		11. Date form reviewed:		
4. Date of visit:			mon	year
day	mon year			
5. Visit code:	_s1			
6. Form & revision:	_rc1_			
7. Study:	NAFLD Database 1			
B. NAFLD Database p	articipation			
8. Date in item 4 of or form:	iginal Database RG			
	mon vegr			

RG - Registration

This is the first form co keyed, before any other When: At first screening Administered by: Clinica Respondent: Patient and	mpleted for a NAFLD Davisit (s1). al Coordinato parent (if pat	NAFI tabase to or. ient is a	D Database forms. age 17 or yo	e patient ounger).	FLD Database and to assign a patient ID The Registration Form must be the first if patient has previously been assigned	st form	
A. Center, patient and	visit identifi	cation		12.	Ethnic category (show the patient/pa	rent Fi	lash
1. Center ID:				-2.	Card #1 and ask the respondent to picture gory that describes the patient best; one):	ck the c	ate-
A D					Hispanic or Latino or Latina	(1)
2. Patient ID:					Not Hispanic, not Latino, not Latina	(2)
3. Patient code:						14.	_ ً
4. Visit date:		=		13.	What describes your Hispanic, Latino, Latina origin best (show the patient/pc Card #1 and ask the respondent to pt category that best describes their His	arent Fl ck the s panic, I	sub-
day	mon		year		ino, or Latina origin; check only one):		,
5. Visit code:	_S	_1			Mexican	(1)
					Puerto Rican	(2)
6. Form & revision:		_r	<u>g</u> _1_		Cuban	(3)
			-		South or Central American	(4)
7. Study:	NAFLD	Data	base_1_		Other Spanish culture or origin	(5)
B. Consent					specify		
 8. Has the patient (or patient's guardian) signed the NAFLD Database informed consent statement: 14. Racial category (show the patient/parent Flash Card #2 and ask the respondent to pick the category or categories that describe the patient best; check all that apply) 						ate-	
		Yes ($\binom{No}{2}$		a. American Indian or Alaska Native:	(1)
		. 1/	STOP		b. Asian:	(1)

C. Information about patient

9.	Date of birth:			
	day –	month	year	
	Record 4-dig	git year for date of bi	irth.	
10.	Age at last bin	rthday:	years	
1.	Gender:			

a. American Indian or Alaska Native:	(1)
b. Asian:	(1)
c. Black, African American, Negro, or Haitian:	(1)
d. Native Hawaiian or other Pacific Islander:	(1)
e. White:	(1)
f. Patient refused:	(1)

15.	In what country was the patient born <i>one</i>):	(check	only	,
	Continental US (includes Alaska) or Hawaii	(1/2)
	Other, (specify):	(2	2)
	specify			-

Male Female

16. Highest educational level achieved b patient (show the patient/parent Flash ask the respondent to pick the cates scribes the patient best; check only of	Card #3 and gory that de-	22. Combined annual income before taxe all members of patient's household (show the patient/parent Flash Care the respondent to pick the category to the patient's continued household.	d #6 and ask hat describes
Never attended school	$\begin{pmatrix} 0 \end{pmatrix}$	the patient's combined household check only one):	income besi;
Kindergarten, pre kindergarten, or	()	Less than \$15,000	(1)
younger	(1)	\$15,000 - \$29,999	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$
Grades 1 to 5	(2)	\$30,000 - \$49,999	$\begin{pmatrix} 2 \\ 3 \end{pmatrix}$
Grades 6-8	(3)	\$50,000 or more	$\begin{pmatrix} & 3 \end{pmatrix}$
Grades 9-11	(4)	\$50,000 of more	(4)
Completed high school	(5)	23. Is the patient under age 18:	
Some college or post high school education or training	(6)	Yes (_ (
Bachelor's degree or higher	$\begin{pmatrix} & & \\ & & \end{pmatrix}$		28.
17. Is the patient currently employed: (Yes 1) (No 2) (20.	24. Current age of patient's mother, stepmother, or female guardian (show patient/parent Flash Card #7 one): Not applicable (mother is deceased of the content of the cont	
18. What is the patient's current occupat	ion:	patient has no stepmother or female guardian)	(0)
		19 or younger	$\begin{pmatrix} & & & & & & & & & & & & & & & & & & &$
specify occupation		20-29 years	
19. About how many hours does the pati-	ent	30-39 years	$\begin{pmatrix} 2 \\ 3 \end{pmatrix}$
work each week:		40-49 years	(4)
	# hours	50-59 years	$\begin{pmatrix} 4 \\ 5 \end{pmatrix}$
20. Which of the following categories be	est	60 years or older	$\begin{pmatrix} & 5 \\ & 6 \end{pmatrix}$
characterizes the patient's occupation history (show the patient/parent Floand ask the respondent to pick the describes the patient best; check only Never employed	nal ash Card #4 category that	25. Highest educational level achieved b patient's mother, stepmother, or femaguardian (show patient/parent Flash education of mother or female guaknown, record as "n"; check only on	y ale h Card #8; if ardian is un-
Laborer	(1)	Never attended school	
Clerical	(₂)	Did not complete high school	$\begin{pmatrix} & 0 \\ & 1 \end{pmatrix}$
Professional	(3)	Completed high school	$\begin{pmatrix} 1 \\ 2 \end{pmatrix}$
Homemaker	(4)	Some college or post high school	(2)
Other, (specify):	(5)	education or training	(3)
		Bachelor's degree or higher	$\begin{pmatrix} & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & \end{pmatrix}$
specify			, 1
21. Marital status of the patient (show the patient/parent Flash Care the respondent to pick the category to the patient best; check only one):			
Single, never married	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
Married or living in marriage-like			
relationship	(2)		
Separated, divorced, or annulled	(3)		
Widowed	(4)		

26. Current age of patient's father, stepfather, or male guardian (show patient/patients) Flash Card #7; check only one):			rent	E. Previous registration in a NASH CRN study nt 29. Has the patient ever been assigned an ID		
	Not applicable (father is deceased or patient has no stepfather or male			number in a NASH CRN study:		
	guardian)	(0	$\begin{pmatrix} \text{Yes} & \begin{pmatrix} \text{No} \\ 1 \end{pmatrix} & \begin{pmatrix} \frac{\text{No}}{2} \end{pmatrix} \end{pmatrix}$		
	19 or younger	Ò	1)	33.		
	20-29 years	$\tilde{}$	2)			
	30-39 years	(3)	30. In which NASH CRN studies has the		
	40-49 years	(3) 4)	patient previously been registered (check all tha apply)		
	50-59 years	(
	•	(5)			
	60 years or older	(6)	b. TONIC: (1)		
27.	Highest educational level achieved by patient's father, stepfather, or male	1 11	0 .6	c. Other, (specify):		
	guardian (show patient/parent Flash Co education of father or male guardian is record as "n"; check only one):	ird #8 unkno	8; if own,	specify		
	Never attended school	(0	31. ID Number previously assigned to patient (record patient ID in item 2):		
	Did not complete high school	(1)	puncin 12 in nem 2).		
	Completed high school	(2)			
	Some college or post high school education or training	(3)	32. Code previously assigned to patient (record patient code in item 3):		
	Bachelor's degree or higher	(4)			
28.	(clinic staff should pick the best descript source of the patient) Source of patient (check only one): Bariatric surgery clinic Current patient of NASH CRN investigator Diabetes clinic GI/liver clinic HMO-based Internal medicine clinic	((((01) 02) 03) 04) 05) 06)	 F. ID assignment (If a STOP condition was checked in section B, the patient is ineligible and a Patient ID should not be assigned. If the patient was previously registered in a NASH CRN study, a new ID number should not be assigned.) 33. Place ID label below and record Patient ID in item 2 and patient code in item 3. 		
	Lipid disorders clinic Liver transplant clinic Obesity clinic	(07) 08)			
	Pediatric clinic	(₀₉)	G. Administrative information		
		(10)	24 Clinical Countington DDU		
	Pediatric weight disorders clinic	(11)	34. Clinical Coordinator PIN:		
	Primary care clinic	(12)	25 (1): 1 (2 1): 4		
	Self referral	(13)	35. Clinical Coordinator signature:		
	Other, (specify):	(14)			
	specify			36. Date form reviewed:		

SD - Liver Biopsy Materials Documentation

Purpose: This form is used **only for biopsies done after Database registration** (i.e., during baseline or followup), or for pre-registration biopsies whose slides were obtained after enrollment. Use forms SE and SF for biopsies done prior to registration in the Database. To document whether liver tissue was obtained for banking and whether the biopsy is adequate for scoring; if adequate for scoring, the number and type of slides available for archival at the DCC is noted. If slides cannot be archived at the DCC, the source of the slides and the date by which the slides that must be returned to the clinical center are recorded.

When: As needed during baseline (visit s1) and followup (visits f024, f048, f096, f144, f192). During followup, specify the code for the followup visit that is currently open (check the patient's visit time window guide). If no window is open (i.e., right after enrollment), or if slides are from a biopsy done prior to registration but were not available until after enrollment, use visit code "n".

By whom: Clinical Coordinator in consultation with the Study Pathologist.

Instructions: This form is used to document acquisition of tissue and slides from liver biopsies done after Database registration (during screening and followup). The SD form provides information about the tissue and slides from the reported biopsy and alerts the DCC to expect completion of the Liver Tissue Banking (LT) form, receipt of tissue at the Biosample Repository, and receipt of slides from the biopsy at the DCC. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and ID code (use labels provided - PATH or PRpt), and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60; the borrowed slides should be labeled on the back of the slide with removable labels with sequence numbers 81-90.

. Center, patient and visit identification			B. Surgical pathology report		
1. Center code:			8. Was a copy of the surgical patholog	y	
2. Patient ID:			report for the biopsy obtained: Ye (+		
3. Patient code:			+ Annotate the report with the po CRN ID number and code (you may pathology labels), black out the po	utient's NASH use one of the	
4. Date form initiated:		and attach the report to this form. * This biopsy cannot be used for the NAFLD			
day	mon	year	Database.		
5. Visit code (s1 or co	ode for followu	p visit that is	9. Biopsy information		
currently open):			a. Date of biopsy specified on the surgical pathology report:		
6. Form & revision:	_S	d3_		year	
7. Study:	NAFLD D	atabase_1_	b. Lobe specimen obtained from <i>(check only one):</i>		
			Right	(1)	
			Left	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	
			Unknown	$\begin{pmatrix} 1 \\ 3 \end{pmatrix}$	

C. Biopsy specimens and stained slides at the clinical center

10. Was a sample of liver tissue obtained for banking:

 $(*_1)$ $(*_2)$ * If Yes, complete the Liver Tissue Banking (LT) form

- 11. Is this visit s1 (ie, a patient currently in screening):

 Yes

 (1)

 (14)
- **12.** Were you able to obtain stained slides from this biopsy for local evaluation and were they adequate for scoring:

Yes $\binom{\text{Yes}}{\binom{+}{1}}$ $\binom{\binom{\text{No}}{*}}{2}$

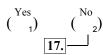
- + Continue with this form and also complete form HF.
- * This biopsy cannot be used for the NAFLD Database.
- **13.** What stained slides from the biopsy are available for local evaluation *(check all that apply)*

a. H & E stain: (1)

b. Masson's trichrome stain: (₁)

D. Unstained slides to be sent to the DCC

14. Are unstained slides available for sending to the DCC:



15. How many unstained slides will be sent to the DCC:

16. What are the slide sequence numbers for those slides *(from the NASH CRN labels on each slide - use permanent labels, sequence numbers 01-60)*

a. Slide sequence number:

01-60

b. Slide sequence number:

01-60

d. Slide sequence number:

c. Slide sequence number:

01-60

e. Slide sequence number:

01-60

f. Slide sequence number:

01-60

g. Slide sequence number:

01-60

h. Slide sequence number:

i. Slide sequence number:

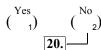
01-60

j. Slide sequence number:

01-60

E. Stained slides to be sent to the DCC

17. Is the institution's H & E stained slide to be sent to the DCC:



18. Slide sequence number for this slide (from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):

81-90

19. Is the H & E stained slide to be returned to the clinical center:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

20. Is the institution's Masson's trichrome stained slide to be sent to the DCC:

(Yes (No 2) (23.)

21. Slide sequence number for slide (from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):

81-90

22. Is the Masson's trichrome slide to be returned to the clinical center:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

23. Is at least one of the stained slides to be returned to the clinical center (i.e., either item 19 = yes or item 22 = yes):

(Yes) (No)

24. When do the stained slides need to be returned to the clinical center *(check only one)*:

Immediately after central review (1)

At the end of the NASH CRN funding period

25. Which pathology department did these slides come from *(check only one):*

NASH CRN clinical center's pathology department

Other, (specify):

name

address

address

phone

Note: this is the Database's record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

F. Administrative information

26. Clinical Coordinator PIN: ____ ___

27. Clinical Coordinator signature:

28. Date form reviewed:

day mon year

SE - Most Recent Prior Liver Biopsy Materials Documentation

Purpose: To document whether the <u>most recent</u> biopsy done prior to Database registation is adequate for scoring; if adequate for scoring, the number and type of slides available for archival at the DCC is noted. If slides cannot be archived at the DCC, the source of the slides and the date by which the slides that must be returned to the clinical center are recorded.

When: As needed during baseline.

By whom: Clinical Coordinator in consultation with the Study Pathologist.

+ Annotate the report with the patient's NASH CRN ID number and code (you may use one of the pathology labels), black out the patient's name,

* This biopsy cannot be used for the NAFLD

and attach the report to this form.

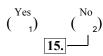
Database.

Instructions: This form is used to document acquisition of slides from the most recent liver biopsy done prior to Database registration and reported on the Baseline Medical History (BG) form. The SE form provides information about slides from the reported biopsy and alerts the DCC to expect receipt of slides from the biopsy. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and ID code (use labels provided - PATH or PRpt), and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60; the borrowed slides should be labeled on the back of the slide with removable labels with sequence numbers 81-90.

a. Center, patient and v	isit identification	9. Date of biopsy sp pathology report:		ical
1. Center code:		day		year
2. Patient ID:		C. Stained slides at tl	he clinical center	
3. Patient code:		10. Were you able to obtain stained slides from this biopsy for local evaluation and		
4. Date form initiated:		were they adequa	Yes (+	$\binom{No}{1}$ $\binom{No}{*}_{2}$
day	mon year			24.
5. Visit code	_s1	HE. * This biopsy o	this form and also c cannot be used for	
6. Form & revision:	<u>s_e_1_</u>	Database.		
7. Study:	NAFLD Database_1_	11. What stained slid available for loca <i>ply)</i>	les from the biopsy il evaluation <i>(checi</i>	
. Surgical pathology re	eport	a. H & E stain:		(1
8. Was a copy of the su report for the biopsy		b. Masson's trich	nrome stain:	(1

D. Unstained slides to be sent to the DCC

12. Are unstained slides available for sending to the DCC:



- **13.** How many unstained slides will be sent to the DCC:
- **14.** What are the slide sequence numbers for those slides *(from the NASH CRN labels on each slide use permanent labels, sequence numbers 01-60)*

a	. :	Slide	seq	uence	num	ber:

	_
01	-60

b. Slide sequence number:

c. Slide sequence number:

d. Slide sequence number:

_		
01	-60	

e. Slide sequence number:

f. Slide sequence number:

g. Slide sequence number:

01-60	

h. Slide sequence number:

٠.	00	
01	-60	

i. Slide sequence number:

	_	

j. Slide sequence number:

01-60	
01-60	

E. Stained slides to be sent to the DCC

15. Is the institution's H & E stained slide to be sent to the DCC:



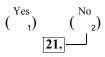
16. Slide sequence number for this slide (from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):

81-90

17. Is the H & E stained slide to be returned to the clinical center:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

18. Is the institution's Masson's trichrome stained slide to be sent to the DCC:



19. Slide sequence number for slide *(from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):*

81-90

20. Is the Masson's trichrome slide to be returned to the clinical center:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

21. Is at least one of the stained slides to be returned to the clinical center (i.e., either item 17 = yes or item 20 = yes):

Yes (No (24.)

22. When do the stained slides need to be returned to the clinical center *(check only one)*:

Immediately after central review

()
(1)

At the end of the NASH CRN funding period

NASH CRN clinical center's pathology

2)

23. Which pathology department did these slides come from *(check only one)*:

department



Other, (specify):



address
address
address

phone

Note: this is the Database's record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

Patient ID:		

F. Administrative information

24. Clinical Coordinator PIN: ____ ___

25. Clinical Coordinator signature:

26. Date form reviewed:

day mon year

NAFLD Database

A

SF - Next Most Recent Prior Liver Biopsy Materials Documentation

Purpose: To document whether the <u>next most recent</u> biopsy done prior to Database registation is adequate for scoring; if adequate for scoring, the number and type of slides available for archival at the DCC is noted. If slides cannot be archived at the DCC, the source of the slides and the date by which the slides that must be returned to the clinical center are recorded.

When: As needed during baseline.

By whom: Clinical Coordinator in consultation with the Study Pathologist.

Instructions: This form is used to document acquisition of slides from the next most recent liver biopsy done prior to Database registration and reported on the Baseline Medical History (BG) form. The SF form provides information about slides from the next more recent prior biopsy and alerts the DCC to expect receipt of slides from the biopsy. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and ID code (use labels provided - PATH or PRpt), and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60; the borrowed slides should be labeled on the back of the slide with removable labels with sequence numbers 81-90.

A. Center, patient and v	visit identification	9. Date of biopsy specified on the surgesthology report:	gical
1. Center code:		day mon	year
2. Patient ID:		C. Stained slides at the clinical center	
3. Patient code:		10. Were you able to obtain stained slice from this biopsy for local evaluation	
4. Date form initiated:		were they adequate for scoring: Ye	$\binom{\text{No}}{1}$ $\binom{\text{No}}{2}$
day	mon year		24.
5. Visit code	_s1	 + Continue with this form and also HG. * This biopsy cannot be used fo 	1 0
6. Form & revision:	<u>s</u> <u>f</u> 1	Database.	
7. Study:	NAFLD Database_1_	11. What stained slides from the biopsy available for local evaluation <i>(chec ply)</i>	
3. Surgical pathology re	eport	a. H & E stain:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
8. Was a copy of the sureport for the biopsy	urgical pathology obtained:	b. Masson's trichrome stain:	(1)
	$\binom{\text{Yes}}{+_{1}} \qquad \binom{\text{No}}{*_{2}}$		
+ Annotate the re CRN ID number and	port with the patient's NASH d code (you may use one of the		

pathology labels), black out the patient's name,

* This biopsy cannot be used for the NAFLD

and attach the report to this form.

Database.

D. Unstained slides to be sent to the DCC

12. Are unstained slides available for sending to the DCC:

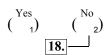
Yes	(No) ()
(1)	15.	2)

- **13.** How many unstained slides will be sent to the DCC:
- **14.** What are the slide sequence numbers for those slides (from the NASH CRN labels on each slide use permanent labels, sequence numbers 01-60)

a.	Slide	sequence	number:
		1	

E. Stained slides to be sent to the DCC

15. Is the institution's H & E stained slide to be sent to the DCC:



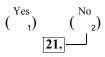
16. Slide sequence number for this slide *(from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):*

81-90

17. Is the H & E stained slide to be returned to the clinical center:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

18. Is the institution's Masson's trichrome stained slide to be sent to the DCC:



19. Slide sequence number for slide *(from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):*

81-90

20. Is the Masson's trichrome slide to be returned to the clinical center:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

21. Is at least one of the stained slides to be returned to the clinical center (i.e., either item 17 = yes or item 20 = yes):

(Yes) (No) (24.

22. When do the stained slides need to be returned to the clinical center (check only one):

Immediately after central review (
At the end of the NASH CRN funding period (

23. Which pathology department did these slides come from *(check only one):*

NASH CRN clinical center's pathology department

Other, (specify):

name
address
address
address
phone

Note: this is the Database's record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

Patient ID:		

F. Administrative information

24. Clinical Coordinator PIN: ____ ___

25. Clinical Coordinator signature:

26. Date form reviewed:

day mon year

Transfer Notification

Purpose: To record a transfer from one center to another center.

When: Upon transferring from the current center and prior to the first visit at the adopting center.

By whom: Clinical coordinator of each center (current center: sections A-C, adopting center: sections D- E).

Instruction: For current center: When patient notifies current center of upcoming transfer, the current clinical coordinator should (1) complete Sections A-C of the Transfer Notification (TN Form), (2) send the TN form to the adopting center, with a copy of the most recent completed HI, LR, and PE/PF forms, (3) send the labels for cryovials and slides and a copy of the visit window schedule to the adopting center. **For adopting center:** Prior to the patient coming to the adopting center, the adopting clinical coordinator should: (1) complete Sections D-E of the TN form, (2) Fax the TN form to the DCC (Fax: 410-955-0932). The DCC will key the form.

A. Current center and patient identification	13. Clinical coordinator signature:		
1. Center ID:			
2. Patient ID:	D. Adopting center, patient and visit identification 14. Adopting center ID:		
3. Patient code:	1 2		
4. Date of notification of intent to transfer:	15. Patient ID (must be same as in Section A):		
day mon year	16. Patient code (must be same as in Section A):		
5. Visit code:	17. Expected date of first followup visit at		
6. Form & revision:tn1	adopting center:		
7. Study: NAFLD Database 1	day mon year		
B. Last followup visit information	18. Visit ID code for expected first followup visit at adopting center:		
8. Date of last followup visit:			
day mon year	Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.		
9. Visit ID code of last completed followup visit:	E. Adopting center administrative information		
	19. Date form reviewed:		
10. Have cryovial and slide labels been sent to the adopting center:	day mon year		
(Yes (No) (*2)) * Send the cryovial and slide labels to the adopting center.	20. Clinical coordinator ID:		
C. Current center administrative information	21. Clinical coordinator signature:		
11. Date form reviewed:			
day mon year	Fax form to the DCC. The DCC will key the TN form.		
12. Clinical coordinator ID:			

NASH CRN PIVENS

PIVENS Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
AN	Serious Adverse Event Report
ВС	Blood Collection for DNA
BD	Food Questionnaire Documentation
BG	Baseline History
BP	Blood Processing for Plasma and Serum
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
DD	DEXA Scan for Bone Mineral Density
DR	Death Report
DX	DEXA Scan for Body Fat
EC	Eligibility Checklist
HF	Liver Biopsy Histology Findings
HI	Follow-up Medical History
HS	Steatohepatitis Determination – 1 st Reading
HT	Steatohepatitis Determination –2 nd Reading
ΙE	Interim Event Report
LD	Lifetime Drinking History (Skinner)
LQ	Symptoms of Liver Disease
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LT	Liver Tissue Banking
LU	Laboratory Results - Tests Required at Visit s2
MV	Missed or Incomplete Visit
PA	Physical Activity
PE	Physical Examination
PF	Focused Physical Examination
QF	MOS 36-Item Short-Form Health Survey
RC	Rescreen Form
RD	Study Drug Dispensing and Return

RG	Registration
SD	Liver Biopsy Materials Documentation
TN	Transfer Notification

A

AD – Alcohol Use Disorders Identification Test (AUDIT)

Keyed: ()

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.

When: Visit s1.

Administered by: Self-administered, but Clinical Coordinator must be available to answer questions and review the completed form.

Respondent: Patient without help from spouse or family.

Instructions: Flash card #7, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to page 2-3 and the Clinical Coordinator then should complete section B below.

. Ce	enter, patient, and vis	it identif	fication			Iministrative info	rmation Clinical Coordin	atov aftav
1.	Center ID:					o be completed by urvey is completed.		ator after
2.	Patient ID:				8.	Clinical Coordin	ator PIN:	
3.	Patient code:	-			9.	Clinical Coordin	ator signature:	
4.	Date of visit:							
	day	mon		year	10.	Date form review	ved:	
5.	Visit code:	<u> </u>	1			day	mon	year
6.	Form & revision:	_	<u>a</u>	<u>d</u> 1				
7.	Study:			PIVENS 2				

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below *(items 1-9 are for clinic use only)*.

11. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times a month	Two to three times a week	Four or more times a week
	01 1033	times a month	tillies a week	tilles a week
$\begin{pmatrix} 0 \end{pmatrix}$	(1)	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	(4)
<u> </u>				

12. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

13. How often do you have six or more drinks on one occasion?

Never Less than monthly		Monthly	Weekly	Daily or almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

14. How often during the last year have you found that you were not able to stop drinking once you had started?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	(1)	(2)	(3)	(4)

15. How often during the last year have you failed to do what was normally expected from you because of drinking?

Never Less than monthly		Monthly	Weekly	Daily or almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

Patient ID:		

16.	How often during the last year have you needed a first drink in the morning to get
	yourself going after a heavy drinking session?

Never Less than monthly		Monthly	Weekly	Daily or almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & 1 \end{pmatrix}$	(2)	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

17. How often during the last year have you had a feeling of guilt or remorse after drinking?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(1)	(2)	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

18. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

19. Have you or someone else been injured as a result of your drinking?

No	Yes, but not in	Yes, during
	the last year	the last year
$\begin{pmatrix} 0 \end{pmatrix}$	(₁)	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

20. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

No	Yes, but not in the last year	Yes, during the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

21. Today's date:

Thank you for completing this questionnaire.

PIVENS

AN - Serious Adverse Event/IND Safety Report

Purpose: To report events that satisfy the IND Safety Report requirements. These include occurrence of a <u>serious</u> (fatal or life-threatening, results in significant or persistent disability, results in a congenital anomaly or birth defect, requires or prolongs hospitalization, or represents other significant hazard or serious harm to research subjects or others) <u>and unexpected</u> (not included in the PIVENS protocol) adverse event that, in the opinion of the investigators, <u>is thought to be associated</u> with PIVENS study drugs.

When: As needed. The AN form should be used <u>only</u> for reporting of a <u>serious and unexpected</u> adverse event which meets the IND Safety Report criteria as stated above is reported, or when a followup report is needed for a previously completed AN form. When the event <u>does not</u> meet the IND Safety Report criteria, use the IE form to report the event.

By whom: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form. The short name (item 25) and the severity code (item 26) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Documents and then click on General Documents. Report the event to your IRB. Send the Data Coordinating Center the following: a copy of this form, a narrative description of the event, and a copy of your report to your IRB. The Data Coordinating Center will submit the report to the FDA (within 15 days) and the DSMB and will circulate the report to the SC.

Followup report: A followup report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patient's condition or in the physician's judgment about the event since the previous report was filed. The Study Physician should use his/her judgment in deciding what is significant and associated with study treatment.

NASH CRN Data Coordinating Center telephone number: (410) 955-8175

A. Center, pat	ient and visit	identificati	on	11. Is the patient currently receiving the pioglitazone-series study drug:	
1. Center ID	:			Yes (Yes	(No 2)
2. Patient ID):			12. Is the patient currently receiving the vitamin E-series study drug:	
3. Patient co	de:			$\binom{\operatorname{Yes}}{1}$	(No 2)
4. Date of re	port:		_	13. Summarize the patient's history of treatment with PIVENS study drugs	
_	day	mon	year	(eg, how long has patient been on study drugs, have there been any treatment	
5. Visit code <i>If report i</i>	e: not associated	with a visit,	fill in ''n.''	interruptions):	
6. Form & re	evision:	_a_	_ n2_		
7. Study:		I	PIVENS 2	-	
B. Participant	information				
8. Date rand	omized in PIV	ENS:			
_	day	mon	year		
9. Gender:					
Male			(1)		
Female			(2)		
10. Age at tim	ne of event:		Vears		

\boldsymbol{C}	Adverse	event	descri	ntior
·.	Auverse	event	uescri	DUUL

14. Is the adverse event associated with PIVENS study drugs both **serious** and **unexpected**: Yes



*A written IND Safety Report will be submitted to the FDA within 15 calendar days by the Project Officer in collaboration with the submitting clinical center and Data Coordinating Center.

†Use PIVENS forms HI, IE, and LR to report adverse events that are not serious, not associated with either series of PIVENS study drugs, or are expected. Do not key this form.

15. Is the adverse event due to the pioglitazone-series study drug:

Definitely yes	(1)
Probably yes	(2)
Possibly yes	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
Probably no	(* 4)
Definitely no	(* ₅)

16. Is the adverse event due to the vitamin E-series study drug:

Definitely yes	(1)
Probably yes	(2)
Possibly yes	(3)
Probably no	(* 4)
Definitely no	(*5)

*If both items 15 and 16 are "no," use PIVENS forms HI, IE, and LR to report adverse events that are not serious, not associated with either series of PIVENS study drugs, or are expected. Do not key this form.

17. Date of event onset:

	<u> </u>	<u></u>
day	mon	year

18. Date event was reported to center:

day	mon	year

19. Describe the event:

20. Non-study medications or supplements in use at the time of event:

21. Specify tests/treatments:

22. Was an unscheduled liver biopsy performed:

Yes	N	Ю
$\begin{pmatrix} * \\ 1 \end{pmatrix}$	(2
e institutional patholo	gy	_

- *Attach a copy of the institutional pathology report to the AN form.
- **23.** Did the event result in significant sequelae:

G	$\binom{\text{Yes}}{1}$	(No 2
Specify:		

24. Is this the first report or a followup report for this adverse event:

First report	(1
Followup report	(2

25.	Short name for adverse event (short a AEs are listed in the CTCAE v3.0 docu able at www.nashcrn.com; click on and then click on General Documents)	ment ave Docume	ail-
26.	Severity grade (severity grades are li CTCAE v3.0 document avai www.nashcrn.com; click on Documen click on General Documents; use oth forms to report adverse events of Gra or Grade 2 (moderate); call the DCG what to do):	lable ts and th er PIVE de l (mi	a t hen NS ild)
	Grade 3 - Severe	(1)
	Grade 4 - Life threatening or	(,
	disabling	(2)
	Grade 5 - Death	(3)
27.	Did the event result in any of the following (check all that apply)		
	a. Emergency department/urgent care visit:	(1)
	b. Hospital admission or prolonged hospital stay:	(1)
	c. Significant or persistent disability:	(1)
	d. Congenital anomaly or birth defect:	(1)
	e. Death:	(1)
	f. Other significant hazard or harm:	(1)
			1/
	g. None of the above	(1)
28.	Current status of adverse event (check	only one	?):
	Resolved	(1)
	Active	(2)
	Unknown	30.] ₃)]
29.	Date resolved:		
	day mon	year	

- **30.** Additional comments on adverse event:
- D. Administrative information
- 31. Study Physician PIN:
- **32.** Study Physician signature:
- 33. Clinical Coordinator PIN:
- **34.** Clinical Coordinator signature:

mon

year

35. Date form reviewed:

Key this form and send the DCC:

day

- (1) A copy of this form(2) A narrative description of the event(3) A copy of your report to your IRB.

BC - Blood Collection for DNA

Purpose: Document the collection of whole blood for shipment to NIDDK Genetics Repository at Rutgers University for DNA extraction. Complete this form only if the patient signed the consent for genetic research.

When: Visit s2, rz, and as needed during followup. You can complete only one BC form prior to randomization. If a redraw of blood is necessary prior to randomization, revise the existing BC form to reflect the most recent blood draw for DNA banking. If redraw is necessary on the day of randomization, complete the BC form with visit code rz but hold the form for keying until after the patient has been randomized (you will not be able to key the form until after the patient has been randomized). If redraw is done after randomization or if the initial draw for DNA is done after randomization (eg, a patient who previously refused consent changes their mind to allow DNA banking), use the visit code for the followup visit whose time window is open. If redraw is done so soon after randomization that a followup visit window is not open, use visit code n.

By whom: Clinical Coordinator and laboratory personnel responsible for collection of whole blood.

A. Center, patient and visit identification

Instructions: (1) Fill two 10 mL EDTA vacutainer tubes with whole blood. (2) Pack and ship the whole blood in the EDTA tubes to the NIDDK Genetics Repository at Rutgers University on the same day blood is collected. Ship at ambient room temperature. Ship whole blood in the specimen shippers supplied by the NIDDK Genetics Repository.

C. Specimen for Genetics Repository

1. Center ID:		each with whole blood; invert each	tube gently 6
2. Patient ID:		times to mix blood with additives; room temperature until the same do the NIDDK Genetics Repository.	
3. Patient code:		• •	-
4. Date of visit:		10. Was blood collected for the NIDDK Genetics Repository:	
	mon year	Yes	(1)
5. Visit code:		No, (specify):	11. (₂)
6. Form & revision:	<u>b</u> <u>c</u> <u>1</u>		
7. Study:	PIVENS_2_	specify	
P. Cl. J			15.
B. Check on consent		11. Date and time of blood draw	
8. Did the patient consen DNA extraction:	t to blood draw for	a. Date:	
21.01 0.00	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{*}_{2}$	b. Time:	year
4.77	(STOP)	hour minute am	1) (₂)
* You cannot proceed until you get consent.		12. Number of 10 mL EDTA tubes:	
9. Did the patient previou	ısly provide blood		
for DNA banking in th	ie NAFLD	13. Form copy of tube labels:	

PIVENS Form BC Pt: ccc- 9999, xyz

> Gender XX

Database:

Patient ID:	
Falletti III.	

T		. •		. •
D. Ad	lministr	ative	infor	mation

15. Clinical Coordinator PIN:

16. Clinical Coordinator signature:

17. Date form reviewed:

day mon year

PIVENS

BD - Food Questionnaire Documentation

Purpose: To document completion of the food questionnaire.

When: Visits s2, f048, f096, and f120. Administered by: Clinical Coordinator.

Instructions: Complete this form after the patient has completed the Block Food Questionnaire. The Block food

questionnaire booklets should be sent to the DCC once a month with the completed TB form.

A. Center, patient, and visit iden	tification
1. Center ID:	
2. Patient ID:	
3. Patient code:	
4. Date form completed <i>(date) booklet is completed):</i>	food questionnaire
day mo	on year
5. Visit code:	
6. Form & revision:	_bd1_
7. Study:	PIVENS 2
B. Administration of food question8. Form copy of label applied to questionnaire:	
PIVENS Form BD Pt: 9999,xyz Visit: vvvv Date:	
C. Administrative information	
9. Clinical Coordinator PIN:	
10. Clinical Coordinator signature	e:
11. Date form reviewed:	_
day mo	on year

PIVENS

BG - Baseline History

Purpose: To collect baseline history information about the patient.

When: Visit s1.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview or chart review. If is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for PIVENS. If is checked for an item, the patient is ineligible and cannot enroll in PIVENS. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

A. Center	wieit	and	nationt	idan	tifica	tion
A. Center	. VISIU.	ana	patient	iaen	unca	uon

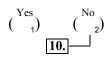
- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: _____ ___
- **4.** Visit date (date this form is initiated):

day	mon	year

- **5.** Visit code: <u>s 1 ___ __</u>
- **6.** Form & revision: <u>b g 3</u>
- 7. Study: PIVENS _2_

B. Family history

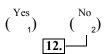
8. Do any of the patient's first degree relatives (parent, brother, sister, child) have liver disease:



- **9.** If yes, characterize the liver disease(s) *(check all that apply)*
 - **a.** Alcohol related liver disease: (1)
 - **b.** Viral hepatitis:
 - c. Alpha-1 antitrypsin deficiency:
 - **d.** Wilson's disease:
 - **e.** Glycogen storage disease:
 - **f.** Iron overload: (₁)
 - **g.** Fatty liver disease (NAFLD, NASH): (1)
 - **h.** Primary liver cancer:
 - i. Type of liver disease unknown:
 - **j.** Other (specify):

specify

10. Do any of the patient's first degree relatives (parent, brother, sister, child) have cirrhosis:



11. If yes, is the cause of the cirrhosis unknown (cryptogenic):

 $\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$

12. Do any of the patient's first degree relatives (parent, brother, sister, child) have diabetes (Type 1 or Type 2):

Yes (1)

No (₂)

Don't know (

13.	Do any of the patient's first degree relatives (parent, brother, sister, child)			18. What procedures/tests supported this fir diagnosis <i>(check all that apply)</i>	st	
	have obesity:			a. Liver biopsy:	(12
	Yes	(1)	b. Imaging studies (Ultrasound, CT, MI	RI): (12
	No	(2)	c. Elevated aminotransferases:	(1
	Don't know	(3)	d. Other (specify):	(
14.	Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:			specify		
	Yes	(1)	D. Weight history		
	No	(2)	b. Weight history		
	Don't know	(3)	19. What was the patient's birthweight:		
15.	Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood fat:			lbs 20. <i>Review flashcard 9.</i> Which (picture) be	oz st	
	Yes	()	describes your weight pattern over the past 5 years (check only one):		
	No	(1) 2)	Up and down, up and down	(`
	Don't know	(2)	Up gradually	(1,
		(3/	Up sharply (gained a lot in a brief inter	val) (2
C. N	NASH history			Down gradually	(3)
16	Date patient was first diagnosed with			Down gradually Down sharply (lost a lot in a brief inter	val) (4) 5)
10.	nonalcoholic steatohepatitis (NASH):			No or minimal change	(5) 6)
17.	day mon What prompted the evaluation for NASH	year		21. What is the patient's current weight (ask the patient for his/her weight):		
	(check all that apply)				lbs	
	a. Symptoms for liver disease:	(1)	22 William and a contract		
	b. Result of being evaluated for another illness:	(1)	22. What is the most the patient has ever weighed:		
	c. During a routine or insurance physical examination:	(1)		lbs	
	d. Blood donation:	(1)	23. At what age did the patient weigh		
	e. Other (specify):	(1)	the most:	ige in ye	oorg
	(1 00)		12	a	ige iii ye	ais
	specify			24. What is the least the patient has		
	1 3			ever weighed since age 18:	lbs	
				25. At what age did the patient weigh the least since age 18:		

age in years

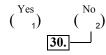
26. Does the patient weigh more than he/she did one year ago:



27. How much more does the patient weigh now compared to one year ago:

 lbs	

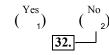
28. Does the patient weigh less than he/she did one year ago:



29. How much less does the patient weigh now compared to one year ago:

·	lbs	

30. Did the patient try to lose or gain weight:



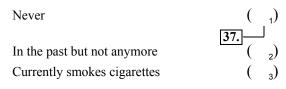
31. Which did the patient try to do *(check only one)*:

Gain weight	(1
Lose weight	(2

E. Tobacco cigarette smoking history

(interview with patient; not by chart review)

32. Have you ever smoked tobacco cigarettes:



33. Did you smoke cigarettes regularly ("No" means less than 20 packs of cigarettes in a lifetime or less than 1 cigarette a day for one year):



34. How old were you when you first started regular cigarette smoking:

 years	

35. How old were you when you (last) stopped smoking cigarettes (code as "n" if the patient didn't stop smoking):

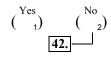
years

36. On the average of the entire time that you smoked cigarettes, how many cigarettes did you smoke per day:

cigarettes/day
cigarettes/day

F. Menstrual history

37. Is the patient female:



38. What was the patient's age at menarche:

age in years

39. Characterize the menstrual history in the past 5 years *(check only one):*

Regular periods	(1) 1)
Irregular periods	(2)
Rare periods	(3
No periods	(

40. Is patient post-menopausal:



41. What was the patient's age at menopause:

age in years

G. Medical history (c means Caution; condition is exclusionary if study physician agrees with diagr. Edema: s. Hepatic encephalopathy: nosis) **42.** Has the patient ever been diagnosed with **t.** Portal hypertension: or treated for any of the following (check all that apply; source of information can be *interview and/or chart review)* **u.** Hepatorenal syndrome: **a.** Diabetes type 1: v. Hepatopulmonary syndrome: **b.** Diabetes type 2: w. Short bowel syndrome: c. Gestational diabetes (diabetes of pregnancy): d. Hepatitis B: **x.** Hemophilia (bleeding disorder): y. Systemic autoimmune disorder such as e. Hepatitis C: rheumatoid arthritis or systemic lupus: z. Endocrine disease **f.** Autoimmune hepatitis: (hormonal abnormality): aa. Hepatocellular carcinoma: g. Autoimmune cholestatic liver disorder (PBC or PSC): **ab.** Other malignancy (cancer): h. Wilson's disease: ac. Human immunodeficiency virus (HIV): i. Alpha-1-antitrypsin (A1AT) deficience ad. Peripheral neuropathy: j. Iron overload: ae. Seizure disorder or epilepsy: **af.** Drug allergies: k. Drug induced liver disease: ag. Hypothyroidism: ah. Hypertension: **I.** Gilbert's syndrome: ai. Cerebrovascular disease: m. Esophageal or gastric varices on endoscopy: aj. Dysbetalipoproteinemia: **n.** Bleeding from varices: ak. Hyperlipidemia (high cholesterol, high triglycerides): al. Pancreatitis: **o.** Other gastrointestinal bleeding:

p. Biliary diversion:

q. Ascites:

am. Cholelithiasis:

an. Coronary artery disease:

	ao. Congestive heart failure:	<u>(c</u>)	1)	45. Has the patient received total parenteral nutrition (TPN) in the past 12 months:
	ap. Elevated uric acid such as gout:		1)	(Yes
	aq. Kidney disease:	(1)	L_(C)(g)
	ar. Polycystic ovary syndrome:	(1)	46. Is the patient currently undergoing
	as. Sleep apnea (not breathing during sleep):	(1)	evaluation for bariatric surgery: Yes
	at. Dermatologic disorders:	(1)	
	au. Myopathy:	(1)	
	av. Myositis:	(1)	H. Drugs historically associated with NAFLD
	aw. Major depression:	(1)	·
	ax. Schizophrenia:	(1)	47. Has the patient used any of the following in the past 2 years
	ay. Bipolar disorder:	(1)	a. Amiodarone (Cordarone, Pacerone):
	az. Obsessive compulsive disorder:	(1)	b. Demeclocycline (Declomycin):
	ba. Severe anxiety or personality disorder:	(1)	c. Divalproex (Depakote):
	bb. Substance abuse:	(1)	d. Doxycycline (Monodox):e. Methotrexate (Rheumatrex):
		<u>/C\</u>		, , , , , , , , , , , , , , , , , , ,
	bc. None of the above:	(1)	f. Minocycline (Dynacin, Minocin):
43.	Has the patient ever had bariatric surg	ery		g. Oxytetracycline (Terramycin):
	for any of the following (check all that			h. Tetracycline (Achromycin):
	a. Stapling or banding of the stomach	: _ (1)	i. Valproate sodium (Depacon):
		<u>/c\</u> —		j. Valproic acid (Depakene):
	b. Jejunoileal (or other intestinal) by	pass: ((₁	k. Other known hepatotoxin (<i>specify</i>):
	c. Biliopancreatic diversion:		(₁	I. None of the above:
	d. Other GI or bariatric surgery (special	ify): (1)	48. Were any of the items on 47a-k checked: $\begin{pmatrix} Yes \\ * \\ * \end{pmatrix}$
	e. None of the above:	(1)	*Caution: Use of any of these draws for mo

*Caution: Use of any of these drugs for more than 2 consecutive weeks in the past 2 years is exclusionary.

44. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver

transplant:

transplant:



49.	Has the patient taken any systemic corticosteroids in the past 2 years (check all that apply):			51. Has the patient taken any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective		
	a. Betamethasone sodium (Celestone):	(1)	estrogen receptor modulators in the past 2 years (check all that apply):		
	b. Cortisol:	(1)	a. Boldenone undecylenate (Equipoise):	(1
	c. Cortisone:	(1)	b. Conjugated estrogen	•	1.
	d. Dexamethasone (Decadron):	(1)	(Premarin/Prempro):	(1.
	e. Hydrocortisone (Hydrocortone):	(1)	c. Diethylstilbestrol and	,	
	f. Methylprednisolone (Solu-Medrol):	(1)	methyltestosterone (Tylosterone):	(1.
	g. Prednisolone (Prelone):	(1)	d. Esterified estrogen (Estratab, Menest):	(1.
	h. Prednisone:	(1)	e. Estradiol (Estrace):	(1.
	i. Triamcinolone (Acetocot, Amcort,			f. Ethinyl estradiol (Estinyl):	(1.
	Aristocort, Kenacort):	(1)	g. Fluoxymesterone (Android-F, Halotestin):	(
	j. Other, (specify):	(1)	h. Levonorgestrel (Norplant):	(1.
	k. Other, (specify):	(1)	i. Medroxyprogesterone (Cycrin, Provera):	(1.
				j. Megestrol (Megace):	(1.
		,	1)	k. Methandrostenolone (Dianabol):	(1
	l. None of the above:	(I. Methyltestosterone (Android):	(1.
50.	Were any of the items 49a-k checked: (Yes (*1)	(¹	No 2	m. Nandrolone (Deca-Durabolin, Durabolin, Hybolin Decanoate, Kabolin):	(1.
	<u></u>			n. Norethindrone (Micronor):	(1
	*Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past 2 years		o. Norgestrel (Ovrette):	(1.	
	is exclusionary.	, .		p. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon, Levlen, Levlite, Levora, Loestrin, Lo-Ovral, Necon, Nelova, Nordette, Norethin, Norinyl, Ortho Cyclen, Ortho-Novum, Ortho Tri-Cyclen, Ovral, Tri-Levlen, Triphasil, Trivora, Zovia):	(1.
				q. Oxandrolone (Oxandrin):	(1.
				r. Oxymetholone (Anadrol):	(1.
				s Progesterone (Prometrium):	(

t. Raloxifene (Evista):u. Stanzolol (Winstrol):v. Tamoxifen (Nolvadex):

w. Testosterone (Depo-Testosterone):

x. Other, (specify):	(1.)
y. Other, (specify):	(1)
z. None of the above:	(1	_

52. Were any of the items 51a-y checked:



*Caution: Use of anabolic steroids, tamoxifen, or estrogens at doses greater than those used for hormone replacement for more than 2 consecutive weeks in the past 2 years is exclusionary.

I. Use of antidiabetic drugs

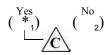
53. Does the patient have a known intolerance for thiazolidinediones (rosiglitazone, pioglitazone):



54.	Has the patient used any antidiabetic
	medications in the past 12 months
	(check all that apply):

q. None of the above:	(1)
p. Other, (specify):	(1)
o. Tolbutamide (Orinase):	(1)
n. Tolazamide (Tolinase):	(1)
m. Rosiglitazone (Avandia):	(1)
l. Repaglinide (Prandin):	(1)
k. Pioglitazone (Actos):	(1)
j. Nateglinide (Starlix):	(1)
i. Miglitol (Glycet):	(1)
h. Metformin (Glucophage, Glucophage XR):	(1)
g. Insulin:	(1)
f. Glyburide (Micronase, DiaBeta, Glynase):	(1)
e. Glipizide (Glucotrol, Glucatrol XL):	(1)
d. Glimepiride (Amaryl):	(1)
c. Chlorpropamide (Diabinese):	(1)
b. Acetohexamide (Dymelor):	(1)
a. Acarbose (Precose):	(1)
(check all that apply):		

55. Were any of the items 54a-p checked:



^{*}Caution: Use of antidiabetic drugs in the 3 months prior to liver biopsy or randomization is exclusionary.

J. Use of antiNASH drugs and vitamins

- **56.** Has the patient taken any of these antiNASH drugs in the past 12 months (check all that apply)
 - a. Betaine (Cystadone):
 - **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler):
 - **c.** Metformin:
 - **d.** Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
 - e. S-adenylmethionine (SAM-e):
 - **f.** Milk thistle:
 - g. Probiotics (any form):
 - h. Gemfibrozil (Gen-Fibro, Lopid):
 - i. Other (specify):

specify

- **j.** None of the above: $\binom{1}{1}$
- 57. Were any of the items in 56a-h checked:



*Caution: Use of antiNASH drugs in the 3 months prior to liver biopsy or randomization is exclusionary.

- **58.** Has the patient taken any antitumor necrosis factor (anti-TNF) therapies in the past 12 months (check all that apply):
 - **a.** Etanercept (Enbrel):
 - **b.** Infliximab (Remicade):
 - **c.** Other, (specify):
 - **d.** None of the above:
- **59.** Were any of the items 58a-c checked:

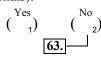


*Caution: Use of anti-TNF therapies in the 3 months prior to liver biopsy or randomization is exclusionary.

60. Has the patient taken a multivitamin regularly in the past 12 months:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

61. Has the patient taken any vitamin E (either as a supplement or in a multivitamin) in the past 12 months):

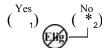


62. Was/Is the dose of vitamin E greater than 100 IU/day:



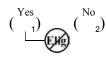
*Caution: Use of vitamin E at more than 100 IU/day in the 3 months prior to biopsy or randomization is exclusionary.

63. Is the patient willing to refrain from taking vitamin E in amounts greater than 100 IU/day during PIVENS:



*Patient may not take vitamin E supplements at doses greater than 100 IU/day during PIVENS.

64. Does the patient have a known intolerance to vitamin E:



65. What other vitamins (other than multivitamins and vitamin E) has the patient taken in the past 12 months (check all that apply):

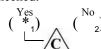
a. Vitamin B (any type):

- **b.** Vitamin C:
- c. Vitamin D:
- **d.** Other, (specify): (1)

e. None of the above:

K. Use of statins, fibrates, and antiobesity drugs

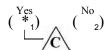
- **66.** Has the patient taken any antihyperlipidemic medications in the past 12 months *(check all that apply):*
 - a. Atorvastatin (Lipitor):
 - **b.** Colestipol hydrochloride (Colestid): (1)
 - **c.** Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)
 - **d.** Fenofibrate (Tricor):
 - e. Fluvastatin sodium (Lescol):
 - **f.** Lovastatin (Mevacor):
 - g. Nicotinic acid (Niaspan):
 - **h.** Pravastatin sodium (Pravachol):
 - i. Rosuvastatin (Crestor):
 - j. Simvastatin (Zocor):
 - **k.** Other, (specify):
 - I. None of the above: (1)
- **67.** Were any of the items 66a-k checked:



1)

*Caution: Use of non-stable doses of statins or fibrates in the 3 months prior to liver biospy or randomization is exclusionary.

- **68.** Has the patient taken any antiobesity medications in the past 12 months (check all that apply):
 - **a.** Dexfenfluramine hydrochloride (Redux):
 - **b.** Fenfluramine hydrochloride (Pondimin):
 - c. Methamphetamine hydrochloride (Desoxyn, Gradumet):
 - **d.** Orlistat (Xenical):
 - **e.** Phendimetrazine tartrate (Adipost, Bontril):
 - **f.** Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
 - g. Sibutramine hydrochloride monohydrate (Meridia): (1)
 - **h.** Other, (specify):
 - i. Other, (specify):
 - **j.** None of the above:
- **69.** Were any of the items 68a-i checked:



*Caution: Use of antiobesity medications in the 3 months prior to randomization is exclusionary.

L. Use of other medications and supplements

70. Has the patient taken any cardiovascula	ar	
or antihypertensive medications in the		
past 12 months that have not already		
been reported on this form (check all the	hat appl	y):
a. Amlodipine besylate (Norvasc):	(1.

aa. Other, (specify):	(1)
z. Other, (specify):	(1)
y. Verapamil (Calan):	(1	1)
x. Valsartan (Diovan):		1)
w. Timolol maleate (Blocadren):	(1)
v. Terazosin (Hytrin):	(1)
u. Quinapril (Accupril):	(1)
t. Propranolol (Inderal):	(1)
s. Perhexiline maleate:	(1)
r. Nifedipine (Adalat, Procardia):	(1)
q. Metoprolol (Lopressor):	(1)
p. Losartan potassium with hydrochlorothiazide (Hyzaar):	(1)
o. Losartan potassium (Cozaar):	(1)
n. Lisinopril (Prinivil, Zestril):		1)
m. Hydrochlorothiazide + triamterene (Dyazide):	(1)
I. Hydrochlorothiazide (Esidrix, HydroDIURIL):	(1)
k. Furosemide (Lasix):	(1)
j. Felodipine (Plendil):	(1)
i. Enalapril (Vasotec):	(1)
h. Doxazosin (Cardura):	(1)
g. Diltiazem (Cardizem):	((((((((((((((((((((1)
f. Digoxin (Lanoxin):		1)
e. Clonidine (Catapres):		1)
d. Captopril (Capoten):		1)
c. Benazepril (Lotensin):		1)
b. Atenolol (Tenormin):	(1)
a. Amlodipine besylate (Norvasc):	(1)
	(1)

71. Has the patient taken any pain relieving	,
non-steroidal anti-inflammatory, or	
aspirin containing medications in the pa	ıst
12 months (check all that apply):	

a. Acetaminophen (Tylenol):	(1.
b. Aspirin - 325 mg:	(1.
c. Aspirin - 81 mg:	(1
d. Celecoxib (Celebrex):	(1
e. Ibuprofen (Advil, Motrin):	(1.
f. Indomethacin (Indocin):	(1.
g. Naproxen (Aleve, Naprosyn):	(1.
h. Rofecoxib (Vioxx):	(1/
i. Valdecoxib (Bextra):	(1/
j. Other, (specify):	(12
k. Other, (specify):	(1,
I. Other, (specify):	(1/
m. None of the above:	(1.

72. Has the patient taken any strong opiates containing acetaminophen medication in the past 12 months (check all that apply)

f. Norco:

a. Darvocet:	(1)
b. Esgic - Plus:	(1)
c. Fioricet:	(1)
d. Lorcet:	(1)
e. Lortab:	(1)

g. Percocet:	(1)
h. Talacen:	(1)
i Tylenol #3:	()

1. Tylenor #3.	(1)
j. Tylenol #4:	(1)
k. Tylox	(.)

K. Tylon.	(1/
l. Vicodin:	(1)
m. Wygesic:	(1)

n. Other, (specify):	(1)

o. None of the above:

73.	Has the patient taken any histamine H2		
	receptor antagonists or other gastrointestinal medications in the past 12 months (check all that apply):		
	a. Cimetidine (Tagamet):	(1)
	b. Esomeprazole magnesium (Nexium):	(1)
	c. Famotidine (Pepcid):	(1)
	d. Lansoprazole (Prevacid):	(1)
	e. Nizatidine (Axid):	(1)
	f. Omeprazole (Prilosec):	(1)
	g. Ranitidine (Zantac):	(1)
	h. Ranitidine bismuth citrate (Tritec):	(1)
	i. Antacids, (specify):	(1)
	j. Other, (specify):	(1)
	k. Other, (specify):	(1)
	l. None of the above:	(1)
74.	Has the patient taken any anticoagulant or antiplatelet medications in the past 12 months (check all that apply):		
	a. Clopidogrel (Plavix):	(1)
	b. Dipyridamole:	(1)
	c. Heparin:	(1)
	d. Ticlopide (Ticlid):	(1)
	e. Warfarin (Coumadin):	(1)
	f. Other, (specify):	(1)
	g. Other, (specify):	(1)
	h. None of the above:	(1)

a. Albuterol:	(
b. Beclomethasone dipropionate (Beclovent, Vanceril):	(
c. Budesonide (Pulmicort, Rhinocort):	(
d. Fluticasone propionate (Flonase, Flovent):	(
e. Loratadine (Claritin):	(
f. Mometasone furoate (Nasonex):	(
g. Triamcinolone acetonide (Azmacort Nasacort):	, (
h. Other, (specify):	(
i. Other, (specify):	(
j. None of the above:	(

76. Has the patient taken any supplements in
the past 12 months that have not already
been reported on this form (check all that apply)

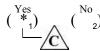
a. Alpha-lipoic acid:	(1)
b. Beta-carotene:	(1)
c. Calcium (any form):	(1)
d. Carnitine (any form):	(1)
e. Chondroitin (any form):	(1)
f. Cod liver oil:	(1)
g. Coenzyme Q:	(1)
h. Dichloroacetate:	(1)
i. Echinacea:	(1)
j. Fish oil (any form):	(1)
k. Flax seed oil:	(1)
I. Garlic:	(1)
m. Ginkgo biloba:	(1)
n. Glucosamine (any form):	(1)
o. Lecithin:	(1)
p. Magnesium:	(1)
q. N-acetyl-cysteine:	(1)
r. Potassium (any form):	(1)
s. Saw palmetto:	(1)
t. Selenium:	(1)
u. St. John's Wort:	(1)
v. Taurine:	(1)
w. Zinc picolinate:	(1)
x. Other, (specify):	(1)
y. Other, (specify):	(1)
z. None of the above:	(1)

77.	Has patient taken any of the following
	medications in the past 12 months
	(check all that apply):

a. Isotretinoin (Accutane):	(1)
b. Levothyroxine (Levoxyl, Synthroid):	(1)
c. Liothyronine (Cytomel):	(1)
d. Penicillamine (Cuprimine, Depen):	(1)
e. Trientine hydrochloride (Syprine):	(1)
f. Other, (specify):	(1)
g. Other, (specify):	(1)
h. Other, (specify):	(1)
i. Other, (specify):	(1)
j. Other, (specify):	(1)
k. None of the above:	(1)

year

- **78.** Has the patient taken any alcohol abuse, inhaled or injection drugs (dependance or withdrawal) medications in the past 12 months (check all that apply):
 - **a.** Chlordiazepoxide (Librium): (1)
 - **b.** Clorazepate dipotassium (Tranxene): (1)
 - **c.** Diazepam (Valium):
 - **d.** Disulfiram (Antabuse):
 - e. Hydroxyzine pamoate (Vistaril):
 - **f.** Naltrexone hydrochloride (Revia):
 - g. Other, (specify):
 - **h.** None of the above: $\begin{pmatrix} 1 \end{pmatrix}$
- **79.** Were any of the items 78a-g checked:



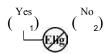
*Caution: Active substance abuse, such as alcohol or inhaled or injection drugs, in the year prior to screening is exclusionary.

M. Willingness to use effective birth control methods

80. Are you female and of childbearing potential:



81. Are you currently pregnant:



82. Are you currently breast feeding:



*Caution: Patient cannot be breastfeeding at time of randomization.

83. Are you willing to use effective birth control methods during PIVENS (ask only females):



N. Administrative information

87. Clinical Coordinator signature:

day

- **84.** Study Physician PIN:
- **85.** Study Physician signature:
- **86.** Clinical Coordinator PIN: ____ ___
- 88. Date form reviewed:

mon

BP - Blood Processing for Plasma and Serum

Purpose: Document collection of fasting blood for local separation of plasma and serum and shipment to NIDDK Biosample Repository at Fisher BioServices.

When: Visits s2, f016, f032, f048, f064, f080, f096, and f120.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of whole blood. **Instructions**: Fill CTAD and SST tubes with whole blood and prepare plasma and serum aliquots in the quantities specified below for the visit. Note that the number of SST tubes used varies by whether or not the patient consented to banking of serum for future research (documented on the Genetic and Future Research Consent Documentation (CG) form (Plasma banking is not affected)).

	All patients		Patients who serum bankin resear	g for future	Patient who consent to ser for future	um banking
	No. of		No. of		No. of	
	4.5 mL	No. of	10 mL	No. of	10 mL	No. of
	CTAD	plasma	SST	serum	SST	serum
Visit	tubes to fill	aliquots	tubes to fill	aliquots	tubes to fill	aliquots
s2	1	5 or 6	4	40	1.5	15
f016	none	none	2	20	none	none
f032	none	none	2	20	none	none
f048	1	5 or 6	4	40	1.5	15
f064	none	none	2	20	none	none
f080	none	none	2	20	none	none
f096	1	5 or 6	4	40	1.5	15
f120	1	5 or 6	3	30	1	10

Label CTAD and SST tubes of whole blood using labels specific for the patient and visit; these labels are generated by the clinic upon registration (screening labels) or after randomization (followup visit labels). Attach duplicate whole blood tube labels in items 12 and 14 below. Process blood for plasma and serum within two hours. After separation, prepare 5 or 6 aliquots of plasma, depending on volume of plasma obtained: transfer 0.5 mL of plasma to each of 5 or 6 (2.0 mL) cryovials. After separation, transfer 0.5 mL of serum to each of the 20 or 40 (2.0 mL) cryovials depending on the visit. Label the plasma and serum cryovials with the numbered patient-specific plasma (blue top) and serum (red top) cryovial labels provided by the DCC. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Affix serum aliquot #00 label (all visits) and plasma aliquot #00 label (if visit s2, f048, f096 or f120) to this form in item 19. The LS code keyed from the cryovial labels in item 19 of this form links the cryovials collected today with the date and visit identified in items 4 and 5 of this form. Freeze labeled aliquots of plasma and serum immediately according to procedures specified in the PIVENS SOP, Part I. NOTE: Immediately upon completion of plasma and serum aliquot preparation, destroy any leftover cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be uniquely identified.

a. Center, patient and visit identification	5. Visit code:	
1. Center code:	6. Form & revision:	_bp1_
2. Patient ID:	7. Study:	PIVENS 2
3. Patient code:		
4. Date of visit:		
day mon year		

Patient ID:		

B. Processing whole blood

Plasma and serum aliquots are to be separated from whole blood per instructions in the SOP. Draw fasting blood in the morning.

8. Was blood collected for the NIDDK Biosample Repository:

Yes	(1)
No, patient was not fasting for 12 hours	(2)
No, other reason (specify):	(4.)—	3)
specify other reason		

9. Date and time of blood draw

a. Date:			
_	day	mon	year
b. Time:	<u> </u>	_ (1)) ()
hour	minute	am	pm

10. Was blood collected for plasma banking at this visit (plasma banking is required at visits s2, f048, f096, and f120):

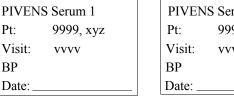


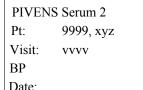
- 11. Number of CTAD (blue-top) tubes:
- **12.** Attach duplicate CTAD tube label:

```
PIVENS Form. BP, Plas.
Pt:
          9999, xyz
Visit
          vvvv
Date: _
```

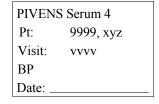
13. Number of SST serum separator (red-top) tubes (4 tubes at visits s2, f048, and f096; 2 tubes at visits f016, f032, f064, and f080; 3 tubes at visit f120):

14. Attach duplicate SST serum separator tube labels:





PIVENS	Serum 3
Pt:	9999, xyz
Visit:	vvvv
BP	
Date:	



15. Phlebotomist:

print name

C. Aliquots for plasma and serum

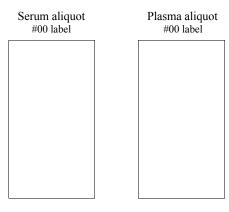
Pour 0.5 mL of plasma into each of up to six 2.0 mL pre-labeled cryovials and pour 0.5 mL of serum into each of forty 2.0 mL pre-labeled cryovials at visits s2, f048, and f096; 20 pre-labeled cryovials at visits f016, f032, f064, and f080; 30 pre-labeled cryovials at visit f120.

16. Date and time of separation into plasma and serum aliquots

	day	mon		year
b. Tim	ne:		(1)	()
-	hour	minute	am	pm

18. Number of aliquots of serum:

19. Attach duplicate cryovial labels (use aliquot 00 labels which are located in the first row of labels for each label set):



20. Technician:

print name

D. Freezing aliquots

Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK BioSample Repository at Fisher BioServices.

21. Date and time cryovials frozen in -70°C or -20°C

a. Date: _			
	day	mon	year
b. Time:		,	

22. Number of cryovials frozen:

minute

- E. Administrative information

hour

- **24.** Clinical Coordinator PIN: ____ ____
- **25.** Clinical Coordinator signature:
- 26. Date form reviewed:

 day mon year

PIVENS

CG - Genetic and Future Research Consent Documentation

Purpose: To document consent for use of DNA samples for genetic research and serum, plasma, and liver tissue samples for future research (Duke, CWRU).

When: Visit s2, rz, or as needed during followup (during followup, use visit code of the followup visit that is open). **By whom**: Study Physician and Clinical Coordinator.

Instructions: Complete this form based on the consent documents signed by the patient. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG form.

A. Center, patient and visit identification

1. Center ID:	
----------------------	--

2. Patient ID:	
-----------------------	--

•	D-4:4 1			
.).	Patient code:			

4.	Date	form	comp	leted

day	mon	year

5.	Visit code:		 	

B. Consent for collection, storage, and use of DNA for current and future genetic research

8. Does the patient consent to genetic research on NASH that is currently planned by the study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

9. Does the patient consent to future genetic research on NASH by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

10. Does the patient consent to future genetic research not related to NASH by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

11. Other information related to consent for genetic research that clinic staff feel needs to be keyed to the study database (e.g., if your genetic consent had other options that are not covered by the 3 categories of use of samples specified above):

12.	In your judgment, has the patient
	consented to collection of blood for DNA
	banking (this question is asked in recognition that
	not all IRBs will have approved consent statements
	that include language that can be mapped into the
	questions in items 8 through 10; a response of
	"No" to this question (item 12) means that blood
	should <u>NOT</u> be collected for sending to the Genet-
	ics Repository and if already collected, should be
	destroyed by the Genetics Repository):

$$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$$

C. Consent for serum, plasma, and liver tissue storage for future research

13. Is this a patient at Duke or CWRU:

$$\begin{pmatrix}
\text{Yes} \\
1
\end{pmatrix} \qquad
\begin{pmatrix}
\text{No} \\
2
\end{pmatrix}$$

14. Does the patient consent to have his/her serum, plasma, and liver tissue stored for future research:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

day

mon

year

PIVENS

CO - Closeout Form

Purpose: To close out a patient's participation in PIVENS and document the patient's consent to join or re-enter the NAFLD Database.

When: At f120 visit or at the close of the f120 window.

Respondent: Clinical coordinator.

Instructions: Complete this form for each patient randomized in PIVENS at the f120 visit or at the close of the f120 window. Determine if the patient now wants to re-enter or join the NAFLD Database. Schedule the patient for a NAFLD Database follow-up visit approximately 6 months from this visit.

(1) Patients previously enrolled in the NAFLD Database: consult the NAFLD Database visit schedule generated at NAFLD enrollment and use the visit window that is open in 6 months (f144 or f192).

(2) Patients NOT previously enrolled in the NAFLD Database: if patient is willing to join the NAFLD Database, a visit schedule will be generated upon keying this form. Schedule the participant approximately 6 months from their PIVENS f120 visit for their f144 NAFLD Database follow-up visit.

	~ .			,			. •
Α.	Center.	natient	and	VISIT	ıden	atifics	itior

- 1. Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ____
- **3.** Patient code: ____ ____
- **4.** Date of visit:

day

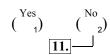
5. Visit code: <u>f</u> <u>1</u> <u>2</u> <u>0</u>

mon

- **6.** Form & revision: <u>c o 1</u>
- 7. Study: PIVENS 2

B. Database participation

8. Does the patient wish to re-enter or join the NAFLD Database:



vear

9. Has the patient signed the latest version of the NAFLD Database informed consent:



* Patient must sign the informed consent

10. Was the patient enrolled in the NAFLD Database previously:

 $\begin{pmatrix} \text{Yes} \\ * \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ + \\ 2 \end{pmatrix}$

* Schedule the patient's next NAFLD Database follow-up visit approximately 6 months from the date in item 4. Consult the patient's NAFLD Database visit schedule and use the NAFLD Database visit open on that date.

+ Data system will generate a visit window schedule assigning the PIVENS randomization date as the NAFLD Database enrollment date. Schedule the patient approximately 6 months from the date in item 4 for their f144 NAFLD Database followup visit.

C. Administrative information

- 11. Clinical Coordinator PIN:
- **12.** Clinical Coordinator signature:

13. Date form reviewed:

day	mon	year

PIVENS

CR - Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Biopsy slides may have visit code s1, f096, or n.

By whom: Data Coordinating Center staff member.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by Data Coordinating Center personnel.

A. Center, participant and visit identification	11. Steatosis (assume macro, e.g., large and small droplet)				
1. Center ID:	a. Grade:				
	< 5%	(0		
2. Patient ID:	5-33%	(1)		
	34-66%	<u>(</u>	2)		
3. Patient code:	> 66%	(3)		
	b. Location:		-		
4. Date of biopsy:	Zone 3	(0		
	Zone 1	(1)		
day mon year	Azonal	(2)		
	Panacinar	(3)		
5. Visit code:	c. Microvesicular steatosis, contiguous patches:				
6. Form & revision:c1	Not present	(0		
	Present	(1)		
7. Study: PIVENS <u>2</u>	12. Fibrosis stage (Masson's trichrome stain)				
B. Central reading	0: None	(0		
8. Date of central reading:	1a: Mild, zone 3, perisinusoidal (requires trichome)	(1)		
day mon year	1b: Moderate, zone 3, perisinusoidal (easily seen on H&E)	(2)		
day mon year	1c: Portal/periportal only	(3)		
9. Which stained slides are available for review <i>(check all that apply)</i>	2: Zone 3 and periportal, any combination	(4)		
a. H & E: (₁)	3: Bridging	(5)		
b. Masson's trichome:	4: Cirrhosis	(6)		
c. Iron: (₁)					
d. Other (specify):					
10. Biopsy length:					

13.	Inflammation				17.	Iron stain		
	 a. Amount of lobular inflamma combines mononuclear, fat granulomas, and pmn foci: 0 < 2 under 20x mag 2-4 under 20x mag > 4 under 20x mag b. Microgranulomas seen: 	ation:	((((0) 1) 2) 3)		 a. Hepatocellular grade: Absent or barely discernible, 40x Barely discernible granules, 20x Discrete granules resolved, 10x Discrete granules resolved, 4x Masses visible by naked eye b. Hepatocellular iron distribution: Periportal 	((((((((((((((((((((0) 1) 2) 3) 4)
	c. Large lipogranulomas seen:	Yes (1)	(2) No 2)		Periportal and midzonal Panacinar Zone 3 or nonzonal c. Sinusoidal lining cell iron grade:	(1) 2) 3)
14.	 d. Amount of portal, chronic inflammation: 0: None 1a: Mild 1b: More than mild Liver cell injury a. Ballooning: 		((0) 1) 2)		None Mild More than mild d. Sinusoidal lining cell iron distribution: Large vessel endothelium only Portal/fibrous bands only, but more than just in large vessel endothelium	((((((((((((((((((((0) 1) 2) 0) 1)
	None Few Many		((0) 1) 2)	18.	Intraparenchymal only Both portal and intraparenchymal Is this steatohepatitis:	(2) 3)
	b. Acidophil bodies:RareManyc. Pigmented macrophages:		(0) 1)		No Suspicious/borderline/indeterminate Yes, definite	(1) 2) 3)
	Rare/absent Many d. Megamitochondria: Rare/absent Many		((0) 1) 0) 1)		Is cirrhosis present: (Yes 1) 21. In the committee's opinion, is this	(¹) —[No 2)
15.	Mallory bodies Rare/absent Many		(0) 1)		cryptogenic cirrhosis: (Yes (1) Other features (check all that apply)	(1	No 2)
16.	Glycogen nuclei: Rare/absent Many		(o) 1)		a. Mallory's hyaline (r/o cholate stasis):b. Perisinusoidal fibrosis away from septa:	(1) 1)
			(1/		c. Hepatocyte ballooning:d. Megamitochondria:e. Other (specify):	((1) 1) 1)
						f. None:	(1)

22. Oth	er comments (spe	ecify):	
_			
_			
_			
_			
	nistrative informating C		
	ature:	enter personner	
24. Date	e form reviewed:		
Dun			

DD - DEXA Scan for Bone Mineral Density

Purpose: To record DEXA scan measurements of bone mineral density.

When: Visits s2, f096, and f120. Administered by: Clinical coordinator.

Instructions: Transfer the DEXA scan measures from your institutional report to Section C. Attach a copy of the

original DEXA report to this form.

A. Center, patient, and visit iden	tification	10. DEXA scanner used:		
		Hologic QDR 4500A	(1)
1. Center ID:		Hologic QDR 4500W	(2)
A D 11 11 11 11 11 11 11 11 11 11 11 11 1		Hologic New Discovery Series 12.3	(3)
2. Patient ID:		Hologic Delphi QDR Series	(4)
2 D .: 1		Hologic Delphi W	(5
3. Patient code:		Lunar Prodigy	(6
4. Date of visit:		Other (specify)	(7)
day mo	on year	specify make & model number		
5. Visit code:		C. DEXA results summary		
6. Form & revision:	<u>d</u> <u>d</u> <u>1</u>	11. Lumbar spine BMD:		
7. Study:	PIVENS 2	g/cm2		
7. Study.		12. Pelvis BMD: •		
B. DEXA scan information		g/cm2		
8. Did the patient have a whole energy x-ray absorptiometry (scan:	(DEXA)	13. Subtotal bone mineral density:		
10	(14. Total bone mineral density:		
9. Reason why DEXA scan was performed <i>(check all that app</i>	oly)	g/cm2 15. Total T-score:	• <u> </u>	
a. Patient is heavier than the weight:	allowed $\begin{pmatrix} 1 \end{pmatrix}$	+ /-		
b. Scanner is broken:	, ,	16. Total Z-score (if available):		
c. Other (specify):	$\begin{pmatrix} & & 1 \\ & & 1 \end{pmatrix}$	+/-		
specify		D. Administrative information		
specify	17.	17. Clinical Coordinator PIN:		
		18. Clinical Coordinator signature:		
		19. Date form reviewed:		

day

mon

year

DR - Death Report

Purpose: To record the report of a patient's death.

When: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete this form whenever the clinical center is informed of a patient's death. If the death is considered associated or possibly associated with participation in the PIVENS study, complete a Serious Adverse Event (AN) form and follow the directions on Form AN for reporting a serious adverse event in PIVENS.

A. Center, patient, and vis	it identi	ficatio	n		10. Place of death:	
1. Center ID:					city/state/country	
2. Patient ID:					city/state/country	
3. Patient code:4. Date form is initiated (a)	late of n	 otice):			11. Cause of death (Study Physician: use whatever knowledge yo have and your best medical judgment to best characterize the cause of death; check only one):	
	mon				Heart disease (1)
uay	IIIOII		year		,	2)
5. Visit code:	_n_					3)
					Malignancy (4)
6. Form & revision:		_d_	<u></u>	1_	Other (specify):	₅)
7. Study:		PIV	/ENS_	2_	specify	_
B. Death information					specify	
8. Date of death:					Unknown (6)
	mon		year		C. Administrative information	
9. Source of death report (check al	ll that	apply):		12. Study Physician PIN:	_
a. Patient's family:			(1)		
b. Friend:			(1)	13. Study Physician signature:	
c. Health care provider staff:	or NAS	H CRI	N (1)	14. Clinical Coordinator PIN:	
d. Newspaper:			(1)		
e. Funeral parlor/home:			(1)	15. Clinical Coordinator signature:	
f. Medical record:			(1)		
g. Medical examiner:			(1)	16. Date form reviewed:	
h. Coroner:			(1)	10. Date form reviewed.	
i. Other (specify):			(1)	day mon year	
oth	er source					
oth	er source					

DX - DEXA Scan for Body Fat

Purpose: To record DEXA scan measurements.

When: Visits s2, f096, and f120. Administered by: Clinical coordinator.

Instructions: Transfer the DEXA scan measures from your institutional report to Section C. Attach a copy of the

original DEXA report to this form.

A. Center, patient, and visit identifi	cation	10. DEXA scanner used:	
1 Conton ID:		Hologic QDR 4500A	(1)
1. Center ID:		Hologic QDR 4500W	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
2. Patient ID:		Hologic New Discovery Series 12.3	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
2. I ditelli ID		Hologic Delphi QDR Series	(4)
3. Patient code:		Hologic Delphi W	(5)
		Lunar Prodigy	(6)
4. Date of visit:		Other (specify)	(7)
day mon	year	specify make & model number	r
5. Visit code:		C. DEXA results summary	
6. Form & revision:	d x 2	11. Date of DEXA scan:	
7. Study:	PIVENS 2	day mon	year
B. DEXA scan information		12. Trunk % fat (if your scanner reports both tissue region % fat, record region % fat on t	% fat and this report):
8. Did the patient have a whole bod energy x-ray absorptiometry (DE scan:			• · · · · · · · · · · · · · · · · · · ·
([10.]	$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$	13. Total % fat (if your scanner reports both tissue region % fat, record region % fat on t	% fat and this report):
9. Reason why DEXA scan was not performed <i>(check all that apply)</i>	t		<u>•</u>
a. Patient is heavier than the alloweight:	owed (1)	D. Administrative information	
b. Scanner is broken:	(1)	14. Clinical Coordinator PIN:	
c. Other (specify):	(1)	15. Clinical Coordinator signature:	
specify			
	14.	16. Date form reviewed:	
		day mon	vear

EC - Eligibility Checklist

Purpose: To check eligibility for PIVENS with respect to items not checked elsewhere on PIVENS screening forms and record reasons for ineligibility for patients found to be ineligible.

When: Visit rz.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: This form may be initiated at any time. If the patient proceeds to randomization, it must be reviewed on the day of randomization. Patients of childbearing potential must complete the randomization day pregnancy test at the clinic on the day of randomization. Patients who are not of childbearing potential may complete the randomization day visit over the telephone. If this is the case, these requirements must be followed:

- (1) If your consent statement has an area for affirmation of consent prior to randomization, the patient should have signed the affirmation at his/her last screening visit.
- (2) The clinical coordinator must confirm with the patient by telephone on the day of randomization, that the patient feels well and continues to consent to randomization.
- (3) The assigned study medication must be mailed to the patient on the day of randomization for delivery the next day.
- (4) The patient should be instructed to start the medications as soon as possible after receipt.

If is checked for any item, complete the entire form, but note that the patient may not continue in the PIVENS trial. If an item has not been assessed because the patient is ineligible, write "m" (missing) next to that item. This form should be keyed for each patient for whom form RG was completed.

Α.	Center.	natient.	visit.	and	study	identification
71.	Cuitti,	paucit	V 1311,	anu	stuuy	iuciitiitatioii

1. Center ID:		

- **2.** Patient ID: ____ __ ___
- **3.** Patient code: ____ ____
- **4.** Visit date (date this form is initiated):

_		_	
day	mon		year

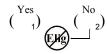
- **5.** Visit code: __r__z______
- **6.** Form & revision: <u>e c 1</u>
- 7. Study: PIVENS 2

B. Alcohol use exclusion

8. On average, has the patient consumed more than 30 g/day of alcohol (males) or 20 g/day of alcohol (females) for a period of more than 3 consecutive months in the 5 years prior to screening:



9. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her (past and current) alcohol intake:

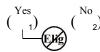


10. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient's alcohol use since starting the screening process consistent with PIVENS eligibility criteria:



C. Cirrhosis exclusion

- 11. Clinical cirrhosis evaluation
 - **a.** Does the patient have varices or ascites <u>and</u> does the physician judge that the patient has cirrhosis:



b. In the Study Physician's judgment, does the patient have cirrhosis (Use histologic, clinical, and laboratory findings such as INR > 1.3, albumin < 3.0 g/dL, or conjugated bilirubin > 2 mg/dL as guidelines):



D. Other chronic liver disease exclusions

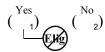
- 12. Evidence of autoimmune liver disease
 - a. Does the patient have ongoing autoimmune liver disease defined by the presence of anti-nuclear antibody (ANA) of greater than 1:80 and liver histology consistent with autoimmune liver disease:



b. In the Study Physician's judgment, does the patient have a history of autoimmune hepatitis:



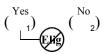
13. Does the patient have primary biliary cirrhosis defined by alkaline phosphatase above the upper limit of normal and anti-mitochondrial antibody (AMA) of greater than 1:80 and liver histology consistent with primary biliary cirrhosis:



14. Does the patient have known primary sclerosing cholangitis and suggestive liver histology:



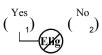
15. Does the patient have Wilson's disease defined by ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



16. Does the patient have alpha-1-antitrypsin (A1AT) deficiency defined by a suggestive liver histology confirmed by A1AT level less than normal (physician judgment):



- 17. Hemochromatosis
 - **a.** Does the patient have a history of hemochromatosis:



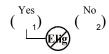
b. Does the patient have a iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:



- **18.** Do any of the patient's assessments show evidence of other chronic liver disease
 - **a.** Drug induced liver disease as defined on the basis of typical exposure and history:



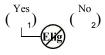
b. Known bile duct obstruction:



c. Suspected or proven liver cancer:



d. Any other type of liver disease other than NASH that warrants exclusion from the trial:

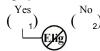


E. Other medical exclusions

19. History of diabetes mellitus:



20. History of bariatric surgery (*jejunoileal bypass or gastric weight loss surgery:*



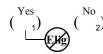
21. History of biliary diversion:



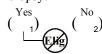
22. Known positivity for antibody to Human Immunodeficiency Virus (HIV):



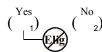
23. Known heart failure of New York Heart Association class 2, 3, or 4:



24. Inability to safely undergo liver biopsy:



25. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the 2 years prior to screening:



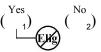
26. Use of antidiabetic drugs in the 3 months prior to randomization:



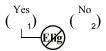
27. Use of antiNASH drugs in the 3 months prior to randomization:



28. Use of a VARIABLE dose of any statins or fibrates in the 3 months prior to randomization:



29. Use of antiobesity drugs in the 3 months prior to randomization:



30. Use of Vitamin E at a dose greater than 100 IU/day:



31. Known active, serious medical disease with a likely life-expectancy less than 5 years:



32. Known active substance abuse, such as alcohol or inhaled or injection drugs in the year prior to screening:

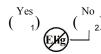


33. Other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study:



F. Birth control exclusion

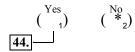
34. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient (females of childbearing potential) willing to use effective birth control methods to avoid pregnancy during the 96 weeks of treatment (check "Yes" if patient is male or not of childbearing potential):



G. Eligibility check on day of randomization

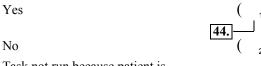
(do in person if patient is of childbearing potential; otherwise, these checks may be done over the telephone with the patient on the day of randomization)

35. Was an ineligibility condition checked or an eligibility not ascertained in items 8-34:



*Key visits s1 and s2 forms RG, AD, BC, BD, BG, BP, CG, DX, HF, HS (if needed), LD, LQ, LR, LS, PA, PE, PF, QF. Run the Randomization Task on your clinic data system.

36. Were any stops or ineligible conditions other than "missing form EC" identified by the Randomization Task:



Task not run because patient is known to be ineligible

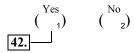


37. Does the patient feel well today:



*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

38. Is the patient male:

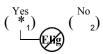


39. Is the patient of childbearing potential:



*Administer pregnancy test.

40. Is the patient pregnant (positive pregnancy test on the day of randomization):



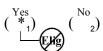
*Go to item 44.

41. Is the patient currently breast feeding



*Go to item 44.

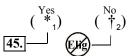
42. Per the Study Physician's judgment, is there any reason to exclude the patient from randomization:



*If Yes, specify reason and then go to item 44:

specify reason

43. Does the patient still consent to randomization (you should ask the patient to orally affirm his/her consent):



*Go to item 45 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.

†Complete items 44-49 and key the form. The form must be keyed to document the reasons for ineligibility for PIVENS.

Н.	Reasons	for	inel	igibil	lity for	· ine	ligi	ble	pat	tients
			_					_		

Note: Complete this section for ineligible patients only.

44.	Reason	for	ineligi	bility	(check	all	that	annlı	,)
77.	ICCason	101	mongi	UTITLY	CHECK	uu	mui	uppi	/

a. Reason covered in items 8-43:

- **b.** Biopsy out of window and patient chose not to repeat: (1)
- **c.** Biopsy inadequate for scoring and patient chose not to repeat: (1)
- **d.** Local pathologist did not find steatohepatitis: (1)
- e. NAS score ≤ 3 or at least 1 subscore = 0: (1)
- **f.** NAS = 4 and central review did not find steatohepatitis: (1)
- **g.** Albumin < 3 g/dL:
- **h.** INR > 1.3:
- i. Bilirubin > 2 mg/dL:
- **j.** Positive for hepatitis B: (1)
- **k.** Positive for hepatitis C: $\binom{1}{1}$
- I. ALT > 300 U/L: $\binom{1}{1}$
- m. Fasting blood glucose ≥ 126 mg/dL: (1) n. Creatinine ≥ 2.0 mg/dL: (1)
- o. Known intolerance to TZDs:
- **p.** Known intolerance to vitamin E:
- q. Liver transplant:
- r. Currently being evaluated for bariatric surgery:
- s. TPN in year prior to screening:
- t. Tests are outside time window and clinic chose not to repeat tests:
- u. Other reason not covered on this form (specify):

-		:	c.
5	pec	L	ιy

I. Administrative information

45. Study Physician PIN:

- **46.** Study Physician signature:
- **47.** Clinical Coordinator PIN:
- **48.** Clinical Coordinator signature:
- ____

49. Date form reviewed

(Note re: patient proceeding to randomization: this form must be reviewed on the day of randomization; if it was keyed prior to the randomization day, update it and re-review it on the day of randomization and key the revised date of review.):

_		_
day	mon	year

(NOTE: If patient was not present in the clinic to receive the assigned medication, send the medication to the patient by overnight delivery service.)

HF - Liver Biopsy Histology Findings

Purpose: Record results of histologic evaluation of slides from liver biopsy for eligibility.

When: Visit s1.

By whom: Study Pathologist at the NASH CRN clinical center (this is not the form used for central reading) and Clinical Coordinator.

Instructions: The Study Pathologist should complete this form using the institution's H & E slide and if available, the institution's Masson's trichrome slide. Upon completion of this form, the Study Pathologist should give the form to the Clinical Coordinator. If fewer than 2 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 2 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the Data Coordinating Center.

If the patient's NASH Activity Score equals 4, review by two additional NASH CRN pathologists is required. Complete forms HS, HT, and IP and send them with the institution's H & E slide to David Kleiner (instructions for shipping are on the IP form). If is checked for any item, the patient is not eligible for PIVENS and the form should not be keyed. If is checked for an item, use caution. If the Study Physician agrees with the diagnosis, the patient is ineligible for PIVENS and the form should not be keyed.

A. Center, patient and visit identification		C. NASH evaluation (use H & E and Masson's trichrome slides only)				
1. Center ID:		• ,				
2. Patient ID:		10. Steatosis (assume macro, e.g., large droplet)	and small	ll		
2. I difent 1D.		a. Grade:				
3. Patient code:		< 5%	·	,)		
4 Data of mar lines		5-33%	(,)		
4. Date of reading:		34-66%	(2	,		
day mon	year	> 66%	(3			
	4	b. Location:				
5. Visit code: <u>S</u>	<u> </u>	Zone 3	(,)		
	1 0 0	Zone 1	(1			
6. Form & revision:	<u>h</u> <u>f</u> 2	Azonal	(2			
7. Study:	PIVENS 2	Panacinar		3)		
		11. Fibrosis stage (Masson's trichrome state	in)			
B. Biopsy information		0: None	(,)		
8. Date this biopsy was performed	(obtained from	1a: Zone 3, perisinusoidal (requires trichome)	_	,)		
surgical pathology report):		1b: Zone 3, perisinusoidal (easily seen	\ 1	,		
day mon	year	on H & E)	(2)		
au inon	year	1c: Portal/periportal only		3)		
9. What slides are to be used in thi evaluation <i>(check all that apply)</i>		2: Zone 3 and periportal, any combination		(,		
a. H & E:	(,	3: Bridging		<u>,</u>		
b. Masson's trichrome:	()	4: Cirrhosis	(6	1		

12.	. Infl	ammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

0



< 2 / 20x mag

2-4 / 20x mag (
> 4 / 20x mag (

b. Amount of portal, chronic inflammation:

None to minimal

Greater than minimal

13. Hepatocellular ballooning:

None



Few Many

(

14. Is steatohepatitis present:

No



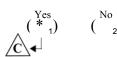
Suspicious/borderline/indeterminate

Yes, definite

(3

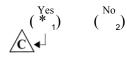
D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:



* Caution: Primary biliary cirrhosis is exclusionary

16. Is there evidence of Wilson's disease:



* Caution: Wilson's disease is exclusionary

17.	Features of chronic cholestatic liver
	disease (check all that apply)

a. Bile duct loss/infiltration/sclerosis:



b. Florid duct lesions:

()

c. Cholate stasis:

 $\begin{pmatrix} 1 \end{pmatrix}$

d. Copper deposition:

 $\begin{pmatrix} 1 \end{pmatrix}$

e. Other (specify):

 $\begin{pmatrix} 1 \end{pmatrix}$

f. None:

1)

* Caution: Bile duct obstruction and primary sclerosing cholangitis are exclusionary

18. Features of other forms of chronic liver disease *(check all that apply)*

a. Vascular lesions of ALD/B-C/OVD:

 $\begin{pmatrix} 1 \end{pmatrix}$

b. Inflammation suggestive of AIH, HCV:



* Caution: Autoimmune liver disease and HCV are exclusionary

c. Pigment suggestive of HH:



* Caution: Hemochromatosis or iron overload as defined by 3+ or 4+ stainable iron is exclusionary

d. Globules suggestive of A1AT:



* Caution: Alpha-1 antitrypsin deficiency is exclusionary

e. Hepatocellular changes suggestive of

HBV:



* Caution: HBV is exclusionary

f. Granulomas suggestive of sarcoid,

PBC, infection:



* Caution: Primary biliary cirrhosis is exclusionary

g. Other (specify):

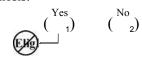
(1

h. None:

1.

Patient ID:		

19. Is there evidence of cirrhosis:



3-8

E. NASH Activity Score

20. NASH activity score (NAS) (sum of items 10a, 12a, and 13)

(Note: each subscore must be 1 or more)

- 21. Is item 20 (NAS) 3 or less: (Yes (No 2)
- 22. Is item 20 (NAS) equal to 4: Yes (*1) (No 2)

* Review by two additional NASH CRN pathologists is required. If there are no ineligibility conditions checked on this form (i.e., the patient is deemed eligible pending determination of steatohepatitis by two additional pathologists), complete forms HS, HT and IP and arrange for review by two additional pathologists.

F. Other comments

23. Other comments:

G. Administrative information

- **24.** Study Pathologist PIN: ____ ___
- 25. Study Pathologist signature:
- **26.** Clinical Coordinator PIN: ____ ___
- **27.** Clinical Coordinator signature:

HI - Followup Medical History

Purpose: To record followup medical history information about the patient. When: Visits f004, f008, f016, f024, f032, f048, f064, f072, f080, f096, and f120. Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview or chart review.

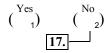
A. Center, visit, and patient identification	D. Alcohol consumption (AUDIT-C) since the last visit (interview with patient)			
1. Center ID:	inst visit (interview with patient)			
2. Patient ID:	11. Since the last visit, how often have you had a drink containing alcohol:			
	Never	(0	
3. Patient code:	14.		_ ا	
	Monthly or less	(1)	
4. Visit date:	Two to four times a month	(2)	
	Two to three times a week	(3)	
day mon year	Four or more times a week	(4)	
 5. Visit code:	12. Since the last visit, how many drinks containing alcohol did you have on a typical day when you are drinking:			
	1 or 2	(0	
7. Study: PIVENS 2	3 or 4	(1)	
	5 or 6	(2)	
B. Interval identification	7 to 9	(3)	
	10 or more	(4)	
8. Date of last Followup Medical History form (if this is visit f004 then date of s1):	13. Since the last visit, how often have you had six or more drinks on one occasion:			
day mon year	Never	(0	
	Less than monthly	(1)	
9. Visit code of last Followup Medical History form (<i>if this is visit f004 then s1</i>):	Monthly	(2)	
Thistory form (y this is visit jood then s1).	Weekly	(3)	
	Daily or almost daily	(4)	
C. NASH evaluation		•	72	

10. Has the patient had a liver biopsy since the last visit:

*Complete the Liver Biopsy Materials Documentation (SD) form.

E. Tobacco cigarette smoking (interview with patient)

14. Since the last visit, have you smoked tobacco cigarettes regularly ("No" means less than I day per week on average):



15. On average, how many days per week have you smoked cigarettes:

days

16. On the days that you smoked, about how many cigarettes did you smoke per day:

cigarettes per day

F. Medical history

17. Since the last visit, has the patient been diagnosed with or treated for any of the following (check all that apply; source of information can be interview and/or chart review; complete an Interim Event Report (IE) form, if any of the conditions checked are possibly or definitely associated with PIVENS study drugs and the event has not already been reported on an IE form)

9		
a. Diabetes type 1:	(1)
b. Diabetes type 2:	(1)
c. Gestational diabetes <i>(diabetes of pregnancy):</i>	(1)
d. Hepatitis B:	(1)
e. Hepatitis C:	(1)
f. Autoimmune hepatitis:	(1)
g. Autoimmune cholestatic liver disorder (PBC or PSC):	(1)
h. Wilson's disease:	(1)
i. Alpha-1-antitrypsin (A1AT) deficiency:	(1)
j. Iron overload:	(1)
k. Drug induced liver disease:	(1)
I. Gilbert's syndrome:	(1)
m. Esophageal or gastric varices on endoscopy:	(1)
n. Bleeding from varices:	(1)
o. Other gastrointestinal bleeding:	(1)
p. Biliary diversion:	(1)

q. Ascites:	(1)	aw. Major depression:	1)
r. Edema:	(1)	ax. Schizophrenia: (1)
s. Hepatic encephalopathy:	(1)	ay. Bipolar disorder: (1)
t. Portal hypertension:	(1)	az. Obsessive compulsive disorder: (1)
u. Hepatorenal syndrome:	(1)	ba. Severe anxiety or personality	,
v. Hepatopulmonary syndrome:	(1)	disorder: (1)
w. Short bowel syndrome:	(1)	bb. Substance abuse:	1)
x. Hemophilia (bleeding disorder):	(1)	bc. None of the above:	1)
y. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:	(1)	18. Since the last visit, has the patient had bariatric surgery for any of the following	
z. Endocrine disease (hormonal abnormality):	()	(check all that apply)	`
aa. Hepatocellular carcinoma:	(1) 1)	a. Stapling or banding of the stomach: (1)
ab. Other malignancy (cancer):	(1)	b. Jejunoileal (or other intestinal) bypass: (1)
	(1)	c. Biliopancreatic diversion: (1)
ac. Human immunodeficiency virus (HIV):	(1)	d. Other GI or bariatric surgery, (specify):	1)
ad. Peripheral neuropathy:	(1)	e. None of the above:	
ae. Seizure disorder or epilepsy:	(1)	e. None of the above.	1)
af. Drug allergies:	(1)	19. Since the last visit, has the patient	
ag. Hypothyroidism:	(1)	received an organ, limb, or bone marrow transplant:	
ah. Hypertension:	(1)		No
ai. Cerebrovascular disease:	(1)	(1) (2)
aj. Dysbetalipoproteinemia:	(1)	20. Since the last visit, has the patient	
ak. Hyperlipidemia (high cholesterol, high triglycerides):	(1)	received total parenteral nutrition (TPN): (Yes (1)	No
al. Pancreatitis:	(1)		
am. Cholelithiasis:	(1)	21. Since the last visit, has the patient been hospitalized <i>(complete an Interim Event Re</i>	port
an. Coronary artery disease:	(1)	(IE) form if possibly or definitely associated PIVENS study drugs and this event has not alre	with
ao. Congestive heart failure:	(1)	been reported on an IE form):	zuuy
ap. Elevated uric acid such as gout:	(1)	$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix}$	No 2)
aq. Kidney disease:	(1)	22.	_ ً
ar. Polycystic ovary syndrome:	(1)	If Yes, specify reason:	
as. Sleep apnea (not breathing during sleep):	(1)	specify	
at. Dermatologic disorders:	(1)		
au. Myopathy:	(1)		
av. Myositis:	(1)		

22. Since the last visit, has the patient had any other health problem not already reported (complete an Interim Event Report (IE) form if possibly or definitely associated with PIVENS study drugs and the event has not already been reported on an IE form):

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	23.

If Yes, specify:

specify

G. Medication use

23. Since the last visit, has the patient used any antidiabetic medications *(check all that apply):*

a. Acarbose (Precose):	(1)
	,	

b. Acetohexamide (Dymelor):	(1)
c. Chlorpropamide (Diabinese):	((۱

	1		`				12
d. Gl	limep	iride	(Amaryl)	:		(1)

e. Glipizide (Glucotrol, Glucatrol XL):	(1)

f. Glyburide (Micronase, DiaBeta,		
Glynase):	(1)

g. Insulin:	(12

h. Metformin (Glucophage,		
Glucophage XR):	(1)
: Miglital (Clysot):	()

i. Migilioi (Glycet).	(1)
j. Nateglinide (Starlix):	(1)

k. Pioglitazone (Actos) (do not include PIVENS study medication):	(1)
		• • • • • • • • • • • • • • • • • • • •

I. Rep	aglinide	(Prandir	n):	(1)
_			•• \	(`

		•
p. Other, (specify):	(1)

q.	None of the above:	(1)

24. Since the last visit, has the patient taken any alcohol abuse (dependance or withdrawal) medications *(check all that apply):*

a.	Chlordiazepoxide (Librium):	(1)
			• • •

g. Other, (specify):
$$\begin{pmatrix} 1 \end{pmatrix}$$

h. None of the above:	(`
II. None of the above.	(1

25. Since the last visit, has the patient taken any antihyperlipidemic medications *(check all that apply):*

a. Atorvastatin (Lipitor):	(1)
\ 1 /		- 1/

b.	Co	lestipol	hydroch	loride	(Colestid):	(1)

c. Clofibrate (Abitrate, Atromid-S,		
Claripex, Novofibrate):	(1)

d. Gemfibrozil (Gen-Fibro, Lopid):	(12
------------------------------------	---	----

20.	Since the last visit, has the patient taken any antiobesity medications (check all that	t apply):		20.	Solution Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing		
	a. Dexfenfluramine hydrochloride (Redux):	(1)		medications (check all that apply):		
	b. Fenfluramine hydrochloride				a. Acetaminophen (Tylenol):	(1)
	(Pondimin):	(1)		b. Aspirin - 325 mg:	(1)
	c. Methamphetamine hydrochloride	(`		c. Aspirin - 81 mg:	(1)
	(Desoxyn, Gradumet): d. Orlistat (Xenical):	(1)		d. Celecoxib (Celebrex):	(1)
	, ,	(1)		e. Ibuprofen (Advil, Motrin):	(1)
	e. Phendimetrazine tartrate (Adipost, Bontril):	(1)		f. Indomethacin (Indocin):	(1)
	f. Phentermine hydrochloride	`	12		g. Naproxen (Aleve, Naprosyn):	(1)
	(Adipex, Fastin, Ionamin, Teramine):	(1)		h. Valdecoxib (Bextra):	(1)
	g. Sibutramine hydrochloride monohydrate (Meridia):	(1)		i. Other, (specify):	(1)
	h. Other, (specify):	(1)		j. Other, (specify):	(1)
	i. Other, (specify):	(1)		k. Other, (specify):	(1)
	j. None of the above:	(1)		I. None of the above:		1)
7.	Since the last visit, has the patient taken any antitumor necrosis factor (anti-TNF) therapies (check all that apply)			29	Since the last visit, has the patient taken any strong opiate medications containing acetaminophen (check all that apply)		
	a. Etanercept (Enbrel):	(1)		a. Darvocet:	(1)
	b. Infliximab (Remicade):	(1)		b. Esgic - Plus:	(1)
	c. Other, (specify):	(1)		c. Fioricet:	(1)
					d. Lorcet:	(1)
	specify d. None of the above:	(`		e. Lortab:	(1)
	d. None of the above.	(1)		f. Norco:	(1)
					g. Percocet:	(1)
					h. Talacen:	(1)
					i. Tylenol #3:	(1)
					j. Tylenol #4:	(1)
					k. Tylox:	(1)
					I. Vicodin:	()
					m. Wygesic:	(1)
					n. Other, (specify):	(1)
					o. None of the above		

	h. None of the above:	(1.
	g. Other, (specify):	(1.
	f. Other, (specify):	(1
	e. Warfarin (Coumadin):	(1.
	d. Ticlopide (Ticlid):	(1
	c. Heparin:	(1.
	b. Dipyridamole:	(1.
	a. Clopidogrel (Plavix):	(1.
31.	Since the last visit, has the patient taken any anticoagulant or antiplatelet medications (check all that apply):		
	I. None of the above:	(1.
	k. Other, (specify):	(1.
	j. Other, (specify):	(1.
	i. Antacids, (specify):	(1.
	h. Ranitidine bismuth citrate (Tritec):	(1
	g. Ranitidine (Zantac):	(1.
	f. Omeprazole (Prilosec):	(1.
	e. Nizatidine (Axid):	(1.
	d. Lansoprazole (Prevacid):	(1,
	c. Famotidine (Pepcid):	(1,
	b. Esomeprazole magnesium (Nexium):	(1,
30.	Since the last visit, has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications <i>(check all that apply):</i> a. Cimetidine (Tagamet):	(1.

b. Cortisol: c. Cortisone: d. Dexamethasone (Decadron): e. Hydrocortisone (Hydrocortone): f. Methylprednisolone (Solu-Medrol): g. Prednisolone (Prelone): h. Prednisone: i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): j. Other, (specify):	
c. Cortisone: d. Dexamethasone (Decadron): e. Hydrocortisone (Hydrocortone): f. Methylprednisolone (Solu-Medrol): g. Prednisolone (Prelone): h. Prednisone: i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): j. Other, (specify):	1)
 d. Dexamethasone (Decadron): (e. Hydrocortisone (Hydrocortone): (f. Methylprednisolone (Solu-Medrol): (g. Prednisolone (Prelone): (h. Prednisone: (i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (j. Other, (specify): (1
e. Hydrocortisone (Hydrocortone): f. Methylprednisolone (Solu-Medrol): g. Prednisolone (Prelone): h. Prednisone: i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): j. Other, (specify):	1
f. Methylprednisolone (Solu-Medrol): g. Prednisolone (Prelone): h. Prednisone: i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): j. Other, (specify): (1)
g. Prednisolone (Prelone): h. Prednisone: (i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (j. Other, (specify): (1)
h. Prednisone: i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (j. Other, (specify): (1)
i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (j. Other, (specify): (1)
Aristocort, Kenacort): (j. Other, (specify): (1)
	1)
k. Other, (specify):	1)
	1)
I. None of the above:	1)

		34. Since the last visit, has the patient taken any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective estrogen recentor modulators.		
(1)	(check all that apply):		
(1)	a. Conjugated estrogen		
(1)	(Premarin/Prempro):	(1)
(1)	b. Diethylstilbestrol and	(`
(1)		(1)
(1)	- '	(1)
(1)	· · ·	(1)
(1)	` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` `	(1)
(1)		(1)
(1)	g. Levonorgestrel (Norplant):	(1)
(1)	h. Medroxyprogesterone (Cycrin,		
(1)	Provera):	(1)
(`	i. Megestrol (Megace):	(1)
(1)	j. Methyltestosterone (Android):	(1)
(1)	k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin):	(1)
(1)	l. Norethindrone (Micronor):	(1)
(1)	m. Norgestrel (Ovrette):	(1)
(1)	 n. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon, 		
(1)	Levlen, Levlite, Levora, Loestrin,		
(1)			
(1)	Ortho-Novum, Ortho Tri-Cyclen,		
(1)		(1)
(1)	•	(1)
(1)	· · · · · · · · · · · · · · · · · · ·	(1)
(1)		(1)
(1)		(1)
(1)	· · · ·	(1)
(1)	t. Other, (specify):	(1)
(1)	u. Other, (specify):	(1)
(1)	v. None of the above:	(1)
		(1) (1)	any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective estrogen receptor modulators (check all that apply): a. Conjugated estrogen (Premarin/Prempro): b. Diethylstilbestrol and methyltestosterone (Tylosterone): c. Esterified estrogen (Estratab, Menest): d. Estradiol (Estrace): e. Ethinyl estradiol (Estinyl): f. Fluoxymesterone (Android-F, Halotestin): g. Levonorgestrel (Norplant): h. Medroxyprogesterone (Cycrin, Provera): i. Megestrol (Megace): j. Methyltestosterone (Android): k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): l. Norethindrone (Micronor): m. Norgestrel (Ovrette): n. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon, Levlen, Levlite, Levora, Loestrin, Lo-Ovral, Necon, Nelova, Nordette, Norethin, Norinyl, Ortho Cyclen, Ovral, Tri-Levlen, Triphasil, Trivora, Zovia): d. Oxandrolone (Oxandrin): p. Oxymetholone (Anadrol): d. Progesterone (Prometrium): r. Raloxifene (Evista): s. Tamoxifen (Nolvadex): t. Other, (specify):	any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective estrogen receptor modulators (check all that apply): (

		40. Since the last visit, has the patient taken any supplements (check all that apply):		
		, , , , , , , , , , , , , , , , , , , ,	(1)
(1)	1 1	(1)
()	c. Betaine (Cystadane):	(1)
(•	d. Calcium (any form):	(1)
(1)	e. Carnitine (any form):	(1)
(1)	f. Chondroitin (any form):	(1)
(1)	g. Choline + methionine + betaine +		
(1)	**	(1)
		h. Cod liver oil:	(1)
(i. Coenzyme Q:	(1)
(1)	j. Dichloroacetate:	(1)
		k. Echinacea:	(1)
(1)	l. Fish oil (any form):	(1)
		m. Flax seed oil:	(1)
(1)	n. Garlic:	(1)
	12	o. Ginkgo biloba:	(1)
a		p. Glucosamine (any form):	(1)
. 1	No \	q. Lecithin:	(1)
(2)	r. Magnesium:	(1)
		s. Milk thistle:	(1)
t		t. N-acetyl-cysteine:	(1)
(1	No)	u. Potassium (any form):	(1)
0. —	2 <i>)</i> _	v. Probiotics (any form):	(1)
<u>. </u>		w. S-adenylmethionine (SAM-e):	(1)
		x. Saw palmetto:	(1)
(.)	y. Selenium:	(1)
(z. St. John's Wort:	(1)
(aa. Taurine:	(1)
(ab. Zinc picolinate:	(1)
((1)
(1)	, (1 33)		12
		ad. Other, (specify):	(1)
		ae. None of the above:	(1)
	(a () () () () () () () () ()	(1) (1) (1) (1) (1) (1) (1) (1)	any supplements (check all that apply): a. Alpha-lipoic acid: b. Beta-carotene: c. Betaine (Cystadane): d. Calcium (any form): e. Carnitine (any form): e. Carnitine (any form): f. Chondroitin (any form): g. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): h. Cod liver oil: i. Coenzyme Q: j. Dichloroacetate: k. Echinacea: l. Fish oil (any form): m. Flax seed oil: o. Ginkgo biloba: p. Glucosamine (any form): g. Lecithin: r. Magnesium: s. Milk thistle: t. N-acetyl-cysteine: u. Potassium (any form): v. Probiotics (any form): v. Probiotics (any form): v. S-adenylmethionine (SAM-e): x. Saw palmetto: y. Selenium: c. St. John's Wort: aa. Taurine: ab. Zinc picolinate: ac. Other, (specify):	any supplements (check all that apply): a. Alpha-lipoic acid: (b. Beta-carotene: (c. Betaine (Cystadane): (d. Calcium (any form): (e. Carnitine (any form): (f. Chondroitin (any form): (f. Chondroitin (any form): (f. Chondroitin (any form): (f. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (h. Cod liver oil: (f. Coenzyme Q: (f. Dichloroacetate: (f. Echinacea: (f. Dichloroacetate: (f. Echinacea: (f. Dichloroacetate: (f. Di

*Remind patient not to take vitamin E supplements at doses greater than 100 IU/day during PIVENS.

- 41. Since the last visit, has the patient taken any of the following medications or other supplements or medications (record all other supplements or medications):
 a. Demeclocycline (Declomycin): (
 b. Divalproex (Depakote): (
 c. Doxycycline (Monodox): (
 d. Isotretinoin (Accutane): (
 e. Levothyroxine (Levoxyl, Synthroid): (
 f. Liothyronine (Cytomel): (
 - g. Methotrexate (Rheumatrex): (
 h. Minocycline (Dynacin, Minocin): (
 - h. Minocycline (Dynacin, Minocin): (1)
 i. Oxytetracycline (Terramycin): (1)
 j. Penicillamine (Cuprimine, Depen): (1)
 - j. Penicillamine (Cuprimine, Depen): (k. Tetracycline (Achromycin): (
 - **k.** Tetracycline (Achromycin): (₁) **l.** Trientine hydrochloride (Syprine): (₁)
 - **m.** Ursodeoxycholic acid (Actigall, Urso, Ursodiol):
 - **n.** Valproate sodium (Depacon):
 - o. Valproic acid (Depakene): (1)p. Other, (specify): (1)
 - q. Other, (specify):
 - r. Other, (specify):
 - s. Other, (specify):
 - t. Other, (specify):
 - **u.** None of the above: (1)

H. Administrative information

- **42.** Study Physician PIN:
- **43.** Study Physician signature:
- **44.** Clinical Coordinator PIN:
- **46.** Date form reviewed:

45. Clinical Coordinator signature:

1) 1)

1)

1)

1)

1)

day	mon	year

HS - Steatohepatitis Determination - 1st Reading

Purpose: To record results of steatohepatitis determination by 1st Pathologist after the local Pathologist scores an entry biopsy with NAS=4 and checks Suspicious/borderline/indeterminate or Definite steatohepatitis on the HF form

When: Visit s1.

By whom: Clinical Coordinator and 1st Pathologist.

Instructions: See instruction sheet.

A. Center, patient, and visit identification	C. Administrati	ve informa	ntion	
1. Center ID:	10. Clinical Coo	ordinator P	IN:	
2. Patient ID:	11. Clinical Cod	ordinator si	gnature:	
3. Patient code:	12. Date form r	eviewed·		
4. Date of visit:		day	mon	
day mon year		uuy	mon	yeur
5. Visit code: _s1				
6. Form & revision: _h_s_1_				
7. Study PIVENS 2				
3. Steatohepatitis determination				
8. Is steatohepatitis present:				
No (₁)				
Suspicious/borderline/indeterminate (2)				
Yes, definite (3)				
9. 1st Pathologist				
a. 1st Pathologist PIN (use initials if no PIN is available):				
b. 1st Pathologist signature:				
c. Date of slide reading:				
day mon year				

HT - Steatohepatitis Determination - 2nd Reading

Purpose: To record results of steatohepatitis determination by 2nd Pathologist after the local Pathologist scores an entry biopsy with NAS=4 and checks Suspicious/borderline/indeterminate or Definite steatohepatitis on the HF form

When: Visit s1.

By whom: Clinical Coordinator and 2nd Pathologist.

Instructions for Clinical Coordinator: See instruction sheet.

A. Center, patient, and vi	C. Administrative information					
1. Center ID:			10. Clinica	al Coordinator	PIN:	
2. Patient ID:			11. Clinica	al Coordinator	signature:	
3. Patient code:			12. Date for	orm reviewed:		
4. Date of visit:						
	mon	 year		Ž		
5. Visit code:	_s1_					
6. Form & revision:	_h_	<u>t</u> 1				
7. Study:	F	PIVENS 2				
. Steatohepatitis determ	ination					
8. Is steatohepatitis pres	ent:					
No		(1)				
Suspicious/borderline	e/indeterminate	(2)				
Yes, definite		(3)				
9. 2nd Pathologist						
a. 2nd Pathologist PI <i>available</i>):	N (use initials	if no PIN is				
b. 2nd Pathologist sig	gnature:					
c. Date of slide reading	ng:					
	mon	year				

IE - Interim Event Report

Purpose: To document events that (1) impact on the patient's treatment or participation in PIVENS (eg, screening liver biopsy complications or temporary or permanent cessation of study medication), or (2) adverse events possibly or definitely associated with study drug that do not meet the criteria for Serious Adverse Event/IND Safety Report (AN) form, or (3) other event that clinical center staff feel should be reported and that is not recorded on another PIVENS form. Adverse events associated with PIVENS study drugs that are both serious and unexpected should not be reported on this (IE) form, but should be recorded on the AN form.

When: As needed; use visit code n even if reporting an event discovered during a regular followup visit. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code n for first event, n1 for second event, etc.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 21) and the severity code (item 22) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Documents and then click on General Documents. Fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher (Fax 410-955-0932).

NASH CRN Data Coordinating Center telephone number: (410) 955-8175.

A. Center, patient, and visit identifi	ication	C. Patient information	
1. Center ID:		9. Date randomized in PIVENS (enter n not yet randomized):	if patient is
2. Patient ID:		day mon	year
3. Patient code:		10. Gender:	
4. Date of report:		Male Female	$\begin{pmatrix} & & \\ & 1 \end{pmatrix}$
day mon	year	11. Age at time of event:	Voorg
5. Visit code:n		12. Is the patient currently receiving the	years
6. Form & revision:	_ie1_	pioglitazone-series study drug: ${\text{Yes} \choose {}_{1}}$	(No
7. Study:	PIVENS 2	13. Is the patient currently receiving the	(2/
B. Visit interval identification		vitamin E-series study drug: $ (\begin{smallmatrix} Yes \\ & 1 \end{smallmatrix})$	(No
8. Most recently completed visit (so or followup)	creening	14. Summarize the patient's history of treatment with PIVENS study drugs (e. has patient been on study drugs, have	g, how long
a. Date:	year	any treatment interruptions):	inere been
b. Visit code:			

D. Event description

15. Is the event associated with PIVENS study drugs:

(Y	es 1)	(No	2)
		18. –		

16. Is the event due to the pioglitazone-series study drug:

Definitely yes	(1
Probably yes	(2
Possibly yes	(3
Probably no	(4)
Definitely no	(5

17. Is the event due to the vitamin E-series study drug:

Definitely yes	(1
Probably yes	(2
Possibly yes	(3
Probably no	(4
Definitely no	(5

18. Date event started:

	<u></u>	
day	mon	year

19. Nature of event *(check all that apply)*

a. Drug dispensing mixup: (1))
---------------------------------------	---

- **b.** Medication related event: (1)
- c. Study procedure related event:
- **d.** Drug interactions: (₁)
- e. Worsening of a co-morbid illness:
- **f.** Patient reported symptom of hepatotoxicity: (1)
- g. Hypoglycemia:
- **h.** New-onset diabetes:
- i. Pregnancy (patient): (*₁
 j. Other (specify): (₁

*PIVENS study drugs will be discontinued if a patient becomes pregnant. Contact the NASH CRN Data Coordinating Center to unmask the study drugs. Complete a Study Drug Dispensing and Return (RD) Form.

20. Describe event:

21. Short name for event if applicable (short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents):

Not applicable (0)

year

22. Severity grade (severity grades are list CTCAE v3.0 document avail www.nashcrn.com; click on Document click on General Documents; use Serious Event Report (AN) to report serious pected adverse events of call the DCC what to do:	lable at s and then us Adverse and unex-
Not applicable	()
Grade 1 - Mild	$\begin{pmatrix} 1 \end{pmatrix}$
Grade 2 - Moderate	(2)
Grade 3 - Severe	$\begin{pmatrix} & & \\ & & & \end{pmatrix}$
Grade 4 - Life threatening or disabling	(4)
Grade 5 - Death	(* 5)
*Complete and key Death Report (DR)	form.
	V
23. Date event resolved <i>(enter n if event resolved):</i>	is not yet
day mon	year
24. What action was taken:	
	
25. Other comments on event:	
·	

E. Administrative information
26. Clinical Coordinator PIN:
27. Clinical Coordinator signature:
28. Study Physician PIN:
29. Study Physician signature:
30. Date form reviewed:

Key this form and fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious events so that we assure appropriate and timely study wide review. The received reports will be reviewed by Jeanne Clark, the Safety Officer, for appropriate further review by the Steering Committee and Data and Safety Monitoring Board.

mon

day

LD – Lifetime Drinking History (Skinner)

Keyed: ()

Purpose: To obtain quantitative indices of the patient's alcohol consumption patterns from the onset of regular drinking

When: Visit s2. If more than one LD form is needed, use visit code "n" on the second LD form.

Administered by: Clinical Coordinator.

Respondent: Patient, without help from spouse or family.

Instructions: In addition to actual consumption levels (quantity), attention is focused upon the frequency of use, variability in consumption, types of beverages, life events that mark a change in drinking pattern, solitary versus social drinking, and time of day when alcohol is consumed. Flash Card #7, Drink Equivalents, may be used with this interview.

The interviewer begins by recording the patient's alcohol consumption behavior during the first year that he/she drank on a regular basis (at least one drink per month). Then, the patient is asked to think of when his/her drinking behavior changed in any appreciable way. In a chronological fashion, the interviewer traces the patient's alcohol consumption behavior from the age of first regular drinking to the present. Flash Card #8, Patterns of Alcohol Intake, provides sample language for the interviewer. Each LD form allows for describing six drinking phases. Use a second LD form (visit code "n") if needed to describe additional drinking phases. If this is the second LD form, skip sections B and C and start with item 20.

The interview takes approximately 20 minutes to complete. It is best given after a reasonable degree of rapport has been established, whereby the patient will feel more at ease and talk openly. Other, considerable probing and cross-referencing of facts is necessary to help in accurate recall. All information should be recorded under the appropriate heading on the LD form.

A. Center, patient, and visit identification

1.	Center ID:				
2.	Patient ID:				
3.	Patient code:				
4.	Date of visit (date p	atient co	mpleted	d the for	m):
	day	mon		y	ear
5.	Visit code:	S			
6.	Form & revision:		<u>l</u>	<u>d</u>	_1_
7.	Study:			PIVE	NS <u>2</u>

B. Lifetime alcohol consumption

8. Over the course of your lifetime have you ever had at least one drink of alcohol, beer, liquor, wine, or wine coolers, per month during a 12-month time period, or at least three drinks per day for at least three consecutive days (over a regular period of time):



Patient ID:		

C. First phase

Read as written: "Now, I am going to ask you about your drinking pattern during the first year that you began to have at least one drink per month until your drinking behavior was different in a significant way from this time."

9. How old were you when you began regular drinking:

a. Years:

yrs

b. Months:

mos

10. How old were you at the end of first stage:

a. Years:

yrs

b. Months:

mos

11. During the first stage, how many drinks would you have on average per occasion (*drinking day*):

drinks

12. How many days per month would you generally drink at this level:

days

13. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

14. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%):

Beer

%

Liquor

%

9/0

15. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent (1)
Occasional (less than 15 days) (2)

Weekend mainly
Binge (at least 3 days heavy drinking) (

Frequent (15 days or more per month)

(4)

16. Did any important event or events occur during this period that altered your usual drinking habits:

Yes No (1) (2)

17. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

Positive Negative Neutral Marital/family . . (3) Work (2) 3) School (c. 2) 3) Medical (1) 2) 3) Residence (e 1) f. Legal/jail (Financial (g. 1) Peer group (h. 1) i. Drug abuse (1) 3) j. Treatment (2) 1) 3) Death (k. 1) 2) 3) Emotional (

18. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%):

Alone

With others

%

%

Patient ID:		

19. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%):

Morning	 %	
Afternoon	 	
Evening	 	

D. Subsequent phase

20. Read as written: "We have just discussed your drinking habits at the point when you first began to drink regularly. Now I want you to think to when your drinking behavior was different in a significant way from this time. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



21. How old were you at the beginning of this phase:

a.	Years:	
		yrs
b.	Months:	
		mos

22. How old were you at the end of this phase:

a.	Y ears:	
		yrs
b.	Months:	
		mos

23. During this phase, how many drinks would you have on average per occasion (*drinking day*):

#	drinks

24. How many days per month would you generally drink at this level (write "m" if not drinking):

# days	

25. What is the most or maximum number of drinks you would have in any one day:

#	drinks	

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

26. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

Beer	 %	
Liquor	 %	
Wine	 <u>%</u>	

27. How would you rate your usual style of drinking during an average month *(check the appropriate category)*:

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	((ء

28. Did any important event or events occur during this period that altered your usual drinking habits:



29. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

0)) 00	/	Positive	Neo	ative	Ne	utral
a.	Marital/family		(2)	(3)
b.	Work	,	Ì	2)	(3)
c.	School	$\begin{pmatrix} 1 \end{pmatrix}$	(2)	(3)
d.	Medical	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)	(3)
e.	Residence	$\begin{pmatrix} 1 \end{pmatrix}$	(2)	(3)
f.	Legal/jail	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)	(3)
g.	Financial	$\begin{pmatrix} 1 \end{pmatrix}$	(2)	(3)
h.	Peer group	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)	(3)
i.	Drug abuse	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)	(3)
j.	Treatment	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)	(3)
k.	Death	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)	(3)
1.	Emotional	(.)	(٠)	(.)

Patient ID:		

30.	What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):	35.	During this pha have on averag
	Alone	36.	How many day drink at this lev
	With others	27	Wiles die de see
31.	During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning,	37.	What is the mo you would have
	afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):		(Note: This is t patient actually his/her potention
	Morning	38.	What type of be
	Afternoon		consume in an percentages of should add up percentages sh
	Evening		Beer
E. Ne	xt subsequent phase		
32.	Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at a subsequent phase. Now I want you to think to when your drinking behavior was		Liquor
	different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits": Yes No	39.	How would you during an avera category);
	81. 4		Abstinent Occasional (les Weekend main

33. How old were you at the beginning of the phase:

34. How old were you at the end of this phase:

a. Years:

b. Months:

a. Years:

b. Months:

35.	During this phase, how many have on average per occasion		
			# drinks
36.	How many days per month we drink at this level (write "m	would yo	ou generally drinking):
			# days
37.	What is the most or maximu you would have in any one d		er of drinks
			# drinks
	(Note: This is the maximum patient actually would drink his/her potential capacity.)		
38.	What type of beverage woul consume in an average mont percentages of beer, liquor of should add up to 100%; if no percentages should all be "to	h <i>(recor</i> or wine; ot drink	d the relative this section
	Beer		<u>%</u>
	Liquor		
	Wine		<u>%</u>

9. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	Ì	5)

yrs

yrs

mos

Patient ID:		

40. Did any important event or events occur during this period that altered your usual drinking habits:

Y	es `	N	lо
(1)	(2)
	42] ←	

41. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Neg	ative	Ne	utral
a.	Marital/family	(1)	(2)	(3)
b.	Work	(1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
g.	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse	(1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
l.	Emotional	((,	ĺ	2)	Ċ	2)

42. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):

Alone	 %	
With others	 %	

43. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 %	
Afternoon	 0%	
Evening	 %	

F. Next subsequent phase

44. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



45. How old were you at the beginning of the phase:

a.	i cais.	
		yrs
h	Months:	
b.	Months:	

46. How old were you at the end of this phase:

a. Years:

			yrs
b.	Months:	_	

47. During this phase, how many drinks would you have on average per occasion (*drinking day*):

# drinks	

48. How many days per month would you generally drink at this level (write "m" if not drinking):

# davs	

49. What is the most or maximum number of drinks you would have in any one day:

	_
#	drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

Patient ID:		

50.	What type of beverage would you usually
	consume in an average month (record the relative
	percentages of beer, liquor or wine; this section
	should add up to 100%; if not drinking,
	percentages should all be "000"):

Beer	 %	
Liquor	 %	
Wine	 %	

51. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	(5)

52. Did any important event or events occur during this period that altered your usual drinking habits:

Yes No



53. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Positi	ive	Nega	ative	Nei	utral
a.	Marital/family	(1)	(2)	(3)
b.	Work	(1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
g.	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse	(1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
l.	Emotional	(1)	(2)	(3)

54.	What percentage of time would you drink alone,
	and what percentage of the time with at least one
	other person (record the relative percentages of
	"Alone" and "With others"; this section should
	add up to 100%; if not drinking, percentages
	should be "000"):

Alone	
With others	

55. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	
Afternoon	
Evening	

G. Next subsequent phase

56. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



- **57.** How old were you at the beginning of the phase:
 - **a**. Years: ______yrs **b**. Months: ______
- **58.** How old were you at the end of this phase:

a. Years:

		yrs
b.	Months:	
		mos

Patient ID:		

59.	During this phase, how many drinks would you have on average per occasion (drinking day): # drinks	65.	What was your perception you say that it had a positiv (undesirable), or neutral (n (for each event that influend drinking pattern, check "1	ve (desirable), negative o) effect on your life need the patient's
60.	How many days per month would you generally drink at this level (write "m" if not drinking):		"2" for negative effect or effect):	"3" for neutral or no
61.	# days What is the most or maximum number of drinks you would have in any one day: # drinks		Pos a. Marital/family . (b. Work (c. School (d. Medical (e. Residence (f. Legal/jail (g. Financial (h. Peer group (itive Negative Neutral 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3) 1) (2) (3)
	(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)		i. Drug abuse (j. Treatment (k. Death (l. Emotional (1) (2) (3) 1) (2) (3)
62.	What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"): Beer	66.	What percentage of time w and what percentage of the other person (record the re "Alone" and "With others add up to 100%; if not drin should be "000"):	time with at least one elative percentages of "; this section should
	Liquor		Alone With others	
	Wine	67.	During what time of the da	
63.	How would you rate your usual style of drinking during an average month <i>(check the appropriate category)</i> ; Abstinent Occasional <i>(less than 15 days)</i>	0 7.	your drinking? Could you of time during the evening, (record the relative percen afternoon and evening; this to 100%; if not drinking, p be "000"):	give me the percentage, afternoon and morning tages of morning, is section should add up
	Weekend mainly Binge (at least 3 days heavy drinking) Frequent (15 days or more per month) (2) (3) (4)		Morning	
64.	Did any important event or events occur during		Afternoon	<u> </u>
	this period that altered your usual drinking habits: Yes No (1) (2) 66.		Evening	%

Patient ID:		

H. Next subsequent phase

68. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":

Yes No () 2 2 81.

69. How old were you at the beginning of the phase:

a. Years:

yrs

b. Months:

mos

70. How old were you at the end of this phase:

a. Years:

yrs

b. Months:

mos

71. During this phase, how many drinks would you have on average per occasion (*drinking day*):

drinks

72. How many days per month would you generally drink at this level (write "m" if not drinking):

days

73. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

4. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

Wine ______

75. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent (1)
Occasional (less than 15 days) (2)
Weekend mainly (3)
Binge (at least 3 days heavy drinking)
Frequent (15 days or more per month) (5)

76. Did any important event or events occur during this period that altered your usual drinking habits:



77. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

	Pos	itive	Neg	gative	Ne	utral
a.	Marital/family (1)	(2)	(3)
b.	Work (1)	(2)	(3)
c.	School (1)	(2)	(3)
d.	Medical (1)	(2)	(3)
e.	Residence (1)	(2)	(3)
f.	Legal/jail (1)	(2)	(3)
g.	Financial (1)	(2)	(3)
h.	Peer group (1)	(2)	(3)
i.	Drug abuse (1)	(2)	(3)
j.	Treatment (1)	(2)	(3)
k.	Death (1)	(2)	(3)
1.	Emotional (Ğ	Ò	á	Ò	<u>.)</u>

Patient ID:		

78.	What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):		
	Alone		
	With others		%
79.	During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):		
	Morning		
	Afternoon		<u>%</u>
	Evening		9/0
. Nu	mber of phases		
80.	Are there any additional s	Y	phases: Yes No
	* If yes, complete a second LD form. Skip sections B and C on second form.		
J. Adr	ministrative information		
81.	Clinical Coordinator PIN	: <u></u>	
82.	Clinical Coordinator signature:		
83.	Date form reviewed:		
	day mo	n	year

PIVENS

LQ – Symptoms of Liver Disease

Purpose: To obtain the patient's view of his/her liver disease symptoms.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered during the visit, but Clinical Coordinator must be available to answer questions and review the form for completeness.

Respondent: Patient.

Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-4. The patient should complete pages 2-4 during the visit. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should then complete section B below.

A. Ce	enter, patient, and vi	isit identificati	on	B. Administrative information	
1.	Center ID:			(To be completed by Clinical Coordinator after survey is completed.)	
2.	Patient ID:			8. Clinical Coordinatora. PIN:	
3.	Patient code:			b. Signature:	
4.	Date of visit:				
	day	mon	year	9. Date form reviewed:	
5.	Visit code:			day mon year	
6.	Form & revision:	<u>l</u>	<u>q</u> 1		
7.	Study:		PIVENS 2		

Affix label here				
Patient ID:				
Patient code:				
Visit code:				

Symptoms of Liver Disease

Instructions: People with liver disease may or may not have symptoms, such as pain over the liver area (right upper quadrant), nausea, poor appetite, itching, tiredness, or fatigue. In this questionnaire, we are trying to identify what symptoms you have, how severe they are, and how much they affect your life style.

(Items 1-9 are reserved for clinical center use.)

10. During the last month, how much have you been bothered by the following: *Circle one for each symptom*

	Degree of bother				
	None at all	A little bit	Moderately	Quite a bit	Extremely
a . Pain over liver (right upper quadrant)	1	2	3	4	5
b . Nausea	1	2	3	4	5
c. Poor appetite	1	2	3	4	5
d. Fatigue	1	2	3	4	5
e. Weight loss	1	2	3	4	5
f. Diarrhea	1	2	3	4	5
g. Muscle aches or cramps	1	2	3	4	5
h. Muscle weakness	1	2	3	4	5
i. Headaches	1	2	3	4	5
j . Easy bruising	1	2	3	4	5
k. Itching	1	2	3	4	5
I. Irritability	1	2	3	4	5
m. Depression/sadness	1	2	3	4	5
n. Trouble sleeping	1	2	3	4	5
o. Trouble concentrating	1	2	3	4	5
p . Jaundice (yellow color to skin, eyes, etc)	1	2	3	4	5
q. Dark urine	1	2	3	4	5
r. Swelling of ankles	1	2	3	4	5
s. Swelling of abdomen	1	2	3	4	5

Affix label here				
Patient ID:	_			
Patient code:	_			
Visit code:	_ [

11. Which of the following best describes your level of fatigue and the effects of your fatigue (choose only one): Circle one I feel completely normal and have no fatigue (circle "1" and go to I have some fatigue, but I can do what I want to do without difficulty 2 I have fatigue and it keeps me from doing what I want to do 4 I have fatigue that prevents me from working and requires that **12.** How frequently are you bothered by fatigue (choose only one):

13. Is your fatigue typically present (choose only one):

14. Is your fatigue typically worse the day after a period of extra activity or exercise:

Affix label here
Patient ID:
Patient code:
Visit code:

15. Do you believe that your fatigue is due to your liver problem (as opposed to something else, like not getting enough sleep, depression or being out of shape):

	Cir	cle oi
	Yes	1
	No	2
6.	In general, how have you felt overall in the past month:	
	Very good	. 1
	Very good	
		. 2
	Good	. 2

Thank you for completing this questionnaire.

PIVENS

LR - Laboratory Results - Tests Done at s1 and During Followup

Purpose: To record archival and current laboratory test results for tests done during both screening and followup. **When**: Visits s1, f002, f004, f008, f012, f016, f024, f032, f040, f048, f056, f064, f072, f080, f088, f096, and f120. **Administered by**: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If we is checked in item 59, the patient is not eligible for PIVENS and the form should not be keyed. Attach copies of the laboratory reports to this form.

A. Center, patient, and visit identification	12. White blood cell count (WBC):
1. Center ID:	$\frac{\bullet}{10^3 \text{ cells/} \mu \text{L or } 10^9 \text{ cells/L}}$
2. Patient ID:	13. Platelet count:
3. Patient code:	, cells/ μL
4. Date of visit:	C. Chemistries Required at visits s1, f024, f048, and f096.
day mon year 5. Visit code:	14. Is metabolic panel required at this visit: (Yes (No 2) 27.
6. Form & revision:	15. Date of blood draw for chemistries:
7. Study: PIVENS _2_	day mon year
B. Hematology Required at visits s1, f024, f048, f096, and f120.	Date must be within the required time window, within 3 months of screening or in the time window for the followup visit (check the patient's PIVENS visit time window guide).
8. Is hematology testing required at this visit:	16. Sodium:
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	mEq/L 17. Potassium:
[14.]——	mEq/L
9. Date of blood draw for complete blood count:	18. Chloride:
day mon year	19. Bicarbonate:
Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's PIVENS visit time window guide).	20. Calcium:
10. Hemoglobin:	21. Phosphate:
g/dL 11. Hematocrit:	22. Blood urea nitrogen (BUN):mg/dL

23.	Creatinine (if serum creatinine $\geq 2.0 \text{ mg/dL}$)
	patient is ineligible):

•	
mg/dL	

24. Uric acid:

•	
 mg/dL	

25. Albumin (if albumin < 3.0 g/dL and physician judges patient has cirrhosis, patient is ineligible):

•	
 g/dL	

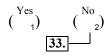
26. Total protein:

•	
 g/dL	

D. Prothrombin time, GGT, and HbA1c

Required at visits f048 and f096.

27. Are the prothrombin time, GGT, and HbA1c tests required a this visit:



28. Date of blood draw for prothrombin time, GGT, and HbA1c:

day	-	mon	year
			for the followu

visit (check the patient's PIVENS visit time window guide).

- **29.** Prothrombin time (PT):
- **30.** International normalized ratio (INR):



31. Gamma glutamyl transferase (GGT):

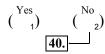
U/L	

32. HbA1c:

E. Liver panel

Required at visits f002, f004, f008, f012, f016, f024, f032, f040, f048, f056, f064, f072, f080, f088, f096, and f120.

33. Is hepatic panel required at this visit:



34. Date of

blood	draw	for liv	er pan	el:	

Date must be in the time window for the followup visit (check the patient's PIVENS visit time window guide).

- 35. Bilirubin (total):
- **36.** Bilirubin (conjugated or direct):

•	
 mg/dL	

37. Aspartate aminotransferase (AST)

	U/L	

- **a.** Upper limit of normal: U/L
- **b.** Lower limit of normal: U/L
- **38.** Alanine aminotransferase (ALT)

 T I /T	

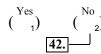
- **a.** Upper limit of normal: U/L
- **b.** Lower limit of normal: U/L
- 39. Alkaline phosphatase U/L
 - a. Upper limit of normal: U/L
 - **b.** Lower limit of normal: U/L

F. Fasting lipid profile

Required at visits \$1, f048, f096, and f120.

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw.

40. Is fasting lipid profile required at this visit:



41. Date of blood draw for fasting lipid profile:

time winaow nt's PIVENS
 mg/dL
 mg/dL
 mg/dL

Date must be within the required time window;

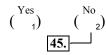
G. Fasting glucose

Required at visits s1, f024, and f072. Also required at visits f048, f096, and f120 if the patient is diabetic.

Fasting is defined as nothing by mouth except water for at least 12 hours prior to blood draw.

42. Is fasting glucose required at this visit:

d. LDL cholesterol level:



mg/dL

43. Date of blood draw for fasting glucose level:

_		_
day	mon	year

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's PIVENS visit time window guide).

44. Serum glucose (if fasting glucose ≥ 126 mg/dL, patient is ineligible):

mg/dL	

H. Oral glucose tolerance test

Required at visits f048, f096, and f120.

The oral glucose tolerance test will be performed in the morning after a 12-hour overnight fasting. Baseline blood sample will be obtained for measurements of serum glucose, insulin, and C peptide. Subsequent blood samples will be obtained every 30 minutes for 120 minutes for the measurement of serum glucose and insulin after oral administration of flavored glucose solution in a dose of 75 g.

45. Is oral glucose tolerance test (OGTT) required at this visit:

Yes	(1)
No	(2)
No, patient is diabetic	52. (₃)
	52.

46. Date of blood draw for OGTT:

_	day	 mon	 -	year

Date must be in the time window for the followup visit (check the patient's PIVENS visit time window guide).

47. OGTT results at baseline

a. Serum glucose:	${mg/dL}$
b. Serum insulin:	<u>μU/mL</u>
c. Serum C peptide:	<u> </u>

ng/mL

48. OGTT results at 30 minutes

a Serum glucose:

a. Seram gracose.	mg/dL
b. Serum insulin:	

49. OGTT results at 1 hour	J. Pregnancy test
a. Serum glucose:	Required at all study visits if applicable.
mg/dL	55. Is pregnancy test applicable:
b. Serum insulin:	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
μU/mL	
50. OGTT results at 90 minutes	58.
a. Serum glucose:	56. Date of urine collection (or blood draw):
${\text{mg/dL}}$	
b. Serum insulin:	day mon year
μU/mL	Date must be the same day as date of visit.
51. OGTT results at 2 hours	57. Pregnancy test result (if pregnancy test is positive at s1, patient is ineligible):
a. Serum glucose: mg/dL	Positive (,)
ilig/uL	Negative (2)
b. Serum insulin: $\underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad}$	IZ DP 9.96 1 1
μU/mL	K. Eligibility check
I. Microalbuminuria	58. Is this the s1 visit:
Required at visits f048, f096, and f120.	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
52. Is microalbuminuria required at this visit:	[1]
$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$	60.
	59. Was the patient found to be ineligible
55.	based on creatinine (item 23), albumin (item 25), serum glucose (item 44), or
53. Date of urine collection for dipstick:	pregnancy test (item 57):
	Yes
day mon year Date must be in the time window for the followup	
visit (check the patient's PIVENS visit time win-	9
dow guide).	L. Administrative information
54. Microalbuminuria:	
Positive (1)	60. Study Physician PIN:
Negative (2)	61. Study Physician signature:
	61. Study Fhysician signature.
	62. Clinical Coordinator PIN:
	63. Clinical Coordinator signature:
	64. Date form reviewed:

year

day

mon

PIVENS

LS - Laboratory Results Tests Done Only During Screening

Purpose: To record archival and current results of laboratory tests done only at screening.

When: Visit s1.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. If is checked for any item the patient is not eligible for the PIVENS trial. If is checked for an item, use caution. If the Study Physician agrees with the diagnosis, the patient is ineligible for PIVENS.

A. Center, patient, and vi	sit identification	B. Screening etiologic tests	
1. Center ID:		8. Date of blood draw for serological a to exclude viral causes of chronic liv	
2. Patient ID:		disease:	_
3. Patient code:	———	day mon Repeat if date is greater than 1 screening.	year year prior to
4. Date of visit:		a. Hepatitis B surface antigen (HBs.	Ag):
	-	Positive	(1)
day	mon year		(Exig)—
5. Visit code:	<u>s</u> 1	Negative	(2)
6. Form & revision:	<u>l s l</u>	b. Hepatitis B core total antibody (anti-HBc) (if total anti-HBc is record results from IgG test):	not available,
7 Ct	PIVENS 2	Positive	(1)
7. Study:		Negative	(₂)
		Not available	$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$
		c. Hepatitis B surface antibody (anti-HBs):	
		Positive	(1)
		Negative	(2)
		Not available	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
		d. Hepatitis C antibody (anti-HCV) sult as negative if EIA is positive negative):	(indicate re- e but RIBA is
		Positive	
		Negative	(2)
		e. Hepatitis C virus RNA (HCV RN	
		Positive	
		Negative	
		Not available	$\begin{pmatrix} & 2 \\ & 3 \end{pmatrix}$

C. Autoantibody studies

9. Date of blood draw for autoantibody studies:

mon

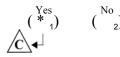
Repeat if date is greater than 5 years prior to screening.

10. Antinuclear antibody (ANA):

Positive

Negative

- a. If positive, ANA: 1/
- * If results are given as units, record as "n" and key the actual result in the General Comments.
- 11. Is ANA titration greater than 1:80



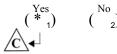
* Check Liver Biopsy Histology Findings Form for autoimmune liver disease.

12. Antimitochondrial antibody (AMA):

Positive Negative

a. If positive, AMA: 1/ * If results are given as units, record as "n" and key the actual result in the General Comments.

13. Is AMA titration greater than 1:80



* Check Liver Biopsy Histology Findings Form for primary biliary cirrhosis.

14. Antismooth muscle antibody (ASMA):

Positive

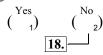
Negative

a. If positive, ASMA: 1/

* If results are given as units, record as "n" and key the actual result in the General Comments.

D. Ceruloplasmin

15. Is patient 40 years old or younger:



16. Date of blood draw for ceruloplasmin:

(required only if patient is 40 years old or younger):

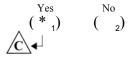
> day mon year

Repeat if date is greater than 10 years prior to screening.

17. Ceruloplasmin



mg/dL b. Is ceruloplasmin below the lower limit of normal:



* Check Liver Biopsy Histology Findings Form for Wilson's Disease.

E. Alpha-1 antitrypsin

18. Date of blood draw for alpha-1 antitrypsin (A1AT):

mon

Repeat if date is greater than 10 years prior to screening.

19. Alpha-1 antitrypsin (A1AT)

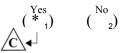
mg/dL

year

a. Lower limit of normal:

mg/dL

b. Is A1AT below the lower limit of normal:



* Check Liver Biopsy Histology Findings Form for A1AT deficiency.

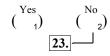
F. Iron

20. Date of blood draw for iron overload screening:

day mon year

Repeat if date is greater than 5 years prior to screening.

- **b.** Total Iron Binding Capacity: _____
- **21.** Is hepoatic iron index available:



G. Administrative information

- 23. Study Physician PIN:
- **24.** Study Physician signature:
- **25.** Clinic Coordinator PIN: ____ ___
- **26.** Clinic Coordinator signature:
- _____
- **27.** Date form reviewed:

=		_
day	mon	year

PIVENS

LT - Liver Tissue Banking

Purpose: To document collection of extra liver tissue and flash freeze procedures for specimen banking.

When: Visits s1 and f096 and as needed for non-protocol biopsies, when more than 2 cm of liver tissue are obtained during a biopsy. This form is expected when the Liver Biopsy Materials Documentation (SD) form says liver tissue was obtained for banking.

By whom: Clinical Coordinator.

Instructions: Liver biopsy tissue should be obtained by a needle core biopsy (as opposed to a wedge biopsy) using a 16 or greater gauge needle. Whenever more than 2 cm of tissue are obtained during biopsy, place a 1-2 mm segment of liver tissue into a 2.0 mL polypropylene cryovial with preprinted label attached. Flash freeze liver tissue immediately (within 5 minutes following biopsy) by placing labeled cryovial containing liver tissue into a portable liquid nitrogen container. Store the cryovial locally in -70° C (or colder) freezer temporarily and batch ship cryovials on dry ice monthly to the NIDDK Biosample Repository located at McKesson Bioservices.

A. Center, patient and visit identification	C. Cryovial label
1. Center ID:	12. Attach duplicate cryovial label (make sure you attach the duplicate of the label attached to the
2. Patient ID:	cryovial holding the liver tissue from this biopsy).
3. Patient code:	
4. Date form initiated:	
day mon year	
5. Visit code (s1 or f096):	-
6. Form & revision:	-
7. Study: PIVENS 2	D. Flash freeze procedures
B. Liver biopsy	13. Was tissue flash frozen within 5 minutes of biopsy by placing in portable liquid nitrogen container:
8. Date of biopsy:	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
day mon year	<u>15.</u>
9. Was the liver tissue obtained using a 16-gauge or greater needle: (Yes (1) (No	Explain what was done and why protocol was not followed:
10. Was liver tissue obtained via a second pass: (Yes (No 2))
11. Was the liver tissue obtained from a	

needle core biopsy (as opposed to a wedge bi-

15. Was tissue shipped on dry ice to the Biosample Repository on same day as biopsy:

(Yes (No 2)

16. Describe conditions of local storage prior to shipment to the Biosample Repository (e.g., temperature, date and time placed in freezer):

E. Administrative information

17. Clinical Coordinator PIN: ____ ___

- **18.** Clinical Coordinator signature:
- 19. Date form reviewed:

 day mon year

LU - Laboratory Results - Tests Required at Visit s2

Purpose: To record archival and current laboratory test results for tests required at visit s2.

When: Visit s2.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If is checked in item 29, the patient is not eligible for PIVENS and the form should not be keyed. Attach copies of the laboratory reports to this form.

A. Center, patient, and visit identification	C. Liver panel		
1. Center ID:	13. Date of blood draw for liver panel:		
2. Patient ID:	day mon Date must be within within 3 mon	year ths of screening.	
3. Patient code:	14. Bilirubin (total):	mg/dL	
4. Date of visit: day mon year	15. Bilirubin (conjugated or direct) (bilirubin > 2 mg/dL and physicia has cirrhosis, patient is ineligible)	if conjugated n judges patient	
5. Visit code:s2	_	mg/dL	
6. Form & revision:	16. Aspartate aminotransferase (AST)	•	
7. Study: PIVENS 2	_		
B. Prothrombin time, GGT, and HbA1c	a. Upper limit of normal:		
8. Date of blood draw for prothrombin time, GGT, and HbA1c:	b. Lower limit of normal:		
day mon year Date must be within 3 months of screening.	17. Alanine aminotransferase (ALT) (> 300 U/L, patient is ineligible)	(if ALT	
9. Prothrombin time (PT):	a. Upper limit of normal:	U/L U/L	
10. International normalized ratio (INR) (if INR > 1.3 and physician judges patient has cirrhosis, patient is ineligible):	b. Lower limit of normal:	U/L	
-	18. Alkaline phosphatase		
11. Gamma glutamyl transferase (GGT):	a. Upper limit of normal:		
12. HbA1c:	b. Lower limit of normal:	U/L	

D. Oral glucose tolerance test

The oral glucose tolerance test will be performed. in the morning after a 12-hour overnight fasting. Baseline blood sample will be obtained for measurements of serum glucose, insulin, and C peptide. Subsequent blood samples will be obtained every 30 minutes for 120 minutes for the measurement of serum glucose and insulin after oral administration of flavored glucose solution in a dose of 75 g.

19.	Date	of bloo	d dray	v for	O	GTT

	_		_
	day	mon	year
_		1 0	

Date must be within 3 months of screening.

20. OGTT results at baseline

a. Serum glucose (if fasting glucose ≥ 126 mg/dL, patient is ineligible):

	/JT	
	mg/dL	

- **b.** Serum insulin: $\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}$

21. OGTT results at 30 minutes

a. Serum glucose:

mg/dL	

b. Serum insulin: $\underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad}$

22. OGTT results at 1 hour

a. Serum glucose:

mg/dL	

23. OGTT results at 90 minutes

a. Serum glucose:

mg/dL	

24. OGTT results at 2 hours

a. Serum glucose:

 mg/dI.	
mg/uL	

b. Serum insulin: $\underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad} \underline{\qquad}$

E. Microalbuminuria

25. Date of urine collection for dipstick:

day	mon	year

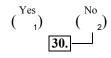
Date must be within 3 months of screening.

26. Microalbuminuria:



F. Pregnancy test

27. Is pregnancy test applicable:



28. Date of urine collection (or blood draw):

=		=
day	mon	year

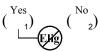
Date must be the same day as date of visit.

29. Pregnancy test results (if pregnancy test is positive, patient is ineligible):

Positive	(1
Negative	(2

G. Eligibility check

30. Was the patient found to be ineligible based on INR (item 10), conjugated (or direct) bilirubin (item 15), ALT (item 17), glucose (item 20a), or pregnancy test (item 29):



H.	Adm	inistr	ative	inform	ation
----	-----	--------	-------	--------	-------

35. Date form reviewed:

31. Study Physician PIN: **32.** Study Physician signature: **33.** Clinical Coordinator PIN: **34.** Clinical Coordinator signature:

mon

year

PIVENS

MV - Missed or Incomplete Visit

Purpose: Record reason(s) for missed or incomplete visit.

When: At the close of a visit window for any missed followup visit or for any followup visit with specific forms not completed.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in missing forms) within the time window for the visit.

A. Center, patient, and visit identification			10. Steps taken to avoid missing the visit (check all that apply)		
1. Center ID:			a. Telephoned patient:	(1)
			b. Mailed reminder card:	(1)
2. Patient ID:			c. Other (specify):	(1)
3. Patient code:			specify		
4. Date form completed:			14.]—	ل
	year		D. Missed form information		
5. Visit code:f			11. Check form(s) not completed (check all that apply)		
6. Form & revision:m	V	2_	a. Food Questionnaire Documentation (BD):	(1)
7. Study: PIVENS_2			b. Blood Processing for Plasma and Serum (BP):	(1)
B. Reason for completion of this form			c. DEXA Scan for Bone Mineral Density (DD):	(1)
8. Was the entire visit missed:			d. DEXA Scan for Body Fat (DX):	(1)
$\binom{\mathrm{Yes}}{1}$	(No 2)	e. Followup Medical History (HI):	(1)
	1.		f. Symptoms of Liver Disease (LQ):	(1)
C. Missed visit information			g. Laboratory Results - Tests Done During Screening and Followup (LR):	(1)
9. Reason for missed visit (check all that ap	pply)		h. Liver Tissue Banking (LT):	(1)
a. Patient was ill:	(1)	i. Physical Activity (PA):	(1)
b. Patient was temporarily away from		17	j. Physical Examination (PE):	(1)
area:	(1)	k. Focused Physical Examination (PF):	(1)
c. Patient refused to return:d. Patient has permanently moved from	(1)	I. MOS 36-Item Short-form Health Survey (QF):	(1)
the area:		1)	m. Study Drug Dispensing and Return		
e. Unable to contact patient:	(1)	(RD):	(1)
f. Other (specify):	(1)	n. Liver Biopsy MaterialsDocumentation (SD):	(1)
	•	•	o. Other (specify):	(1)
specify					
			specify		

12.	Reason form(s) not completed (check all that apply)		
	a. Patient was ill:	(1.
	b. Patient refused procedure:	(1.
	c. Procedure forgotten:	(1.
	d. Other (specify):	(1.
	specify		
13.	Attempts made to complete form(s) (check all that apply)		
	a. Attempted to reschedule procedure:	(1.
	b. Attempted to collect interview data by phone from patient:	(1.
	c. Attempted to gain patient cooperation:	(1.
	d. Other (specify):	(1.
	specify		
E. A	Administrative information		
14.	Clinical Coordinator PIN:		
15.	Clinical Coordinator signature:		
16.	Date form reviewed:		
	day mon	year	

PA – Physical Activity

Keyed: ()

Purpose: To obtain the patient's physical activity.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered, but Clinical Coordinator must be available at visits to answer questions and review the completed form.

Respondent: Patient, without help from spouse or family.

Instructions: The Clinical Coordinator should complete section A below and attach a label to each of pages 2-4. **Screening:** The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-4. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should complete section B below. **Followup:** Pages 2-4 may be mailed to the patient 2 weeks prior to the scheduled study visit with instructions to complete the form at home and to bring the completed form to the next study visit. When the patient returns for the visit, the Clinical Coordinator should review the form for completeness and obtain responses for missing items during the visit. If the patient did not bring a completed form to the visit, the patient should complete the form at the visit. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should complete section B. Item 4 should be completed with the date the patient wrote in item 39. If the patient did not write in a date, use the date of the study visit for the visit date.

	enter, patient, and v	isit identificati	on	(T	o be comp			dinator after	
1.	Center ID:	<u> </u>		SU	rvey is cor	прівіва.)			
2.	Patient ID:			8.	Clinical (Coordinator			
3.	Patient code:					nature:			
4.	Date of visit (date p	patient complete	ed the form):						
				9.	Date form	n reviewed:			
	day	mon	year						
5.	Visit code:				day		mon	year	
6.	Form & revision:	p_	_a_1_						
7.	Study:		PIVENS 2						

Affix label here					
Patient ID:	i				
Patient code:					
Visit code:					

PA - Physical Activity

Instructions: This survey asks for your views about your physical activity. (*Items 1-9 are reserved for clinical center use*).

C. Non-Recreational Activity (Work Related)

The following questions are about your non-recreational activity. Non-recreational activity is what you consider your main day to day activity, at work or at home, whether you get paid or not.

10.	Circle one Level of activity that best describes your usual non-recreational activity.
	Vigorous or strenuous activity:
	Moderate activity:
	(requires moderate-paced walking on a flat surface, heavy one-arm work or moderate two-arm work, such as picking, sweeping, lifting light objects, or heavy housework)
	Light activity:
11.	On average, how many hours per day do you spend at this level of activity?
	Hours
12.	On average, how many hours per day do you spend sitting down?
	Hours

Affix label here
Patient ID:
Patient code:
Visit code:
L

D. Recreational Activity (Non-Work Related)

The following questions are about the recreational activities you spend at least 15 minutes doing each week. You should count walking or biking to work and any other activities outside of work. Next to each activity that you participate in, write in how many total hours or minutes you do that activity on an average week. Mark the places for hours and minutes only for the activities you participate in.

	For each activity that you engage in for at least 15 minutes per week, please circle the activity and write the number of hours or minutes that you do that activity per week.					
13.	Swimming	Hours:	Minutes:			
14.	Jogging		Minutes:			
15.	Running	Hours:	Minutes:			
16.	Brisk walking	Hours:	Minutes:			
17.	Bicycling on hills	Hours:	Minutes:			
18.	Bicycling on flat surfaces	Hours:	Minutes:			
19.	Hiking or climbing	Hours:	Minutes:			
20.	Yard work / Gardening	Hours:	Minutes:			
21.	Aerobics	Hours:	Minutes:			
22.	Dancing	Hours:	Minutes:			
23.	Calisthenics (exercises without machines)	Hours:	Minutes:			
24.	Weight lifting, using weight machines, or heavy lifting	Hours:	Minutes:			
25.	Treadmill or Stairmaster	Hours:	Minutes:			
26.	Chopping wood	Hours:	Minutes:			

Affix l	abel here
Patient ID:	
Patient code:	<u> </u>
Visit code:	
i	

For each activity that you engage in for at least 15 minutes per week, please circle the activity and write the number of hours or minutes that you do that activity per week.				
27.	Painting / Woodworking	Hours:	Minutes:	
28.	Housecleaning	Hours:	Minutes:	
29.	Golfing	Hours:	Minutes:	
30.	Singles tennis, racquetball, or other court sports	Hours:	Minutes:	
31.	Doubles tennis, racquetball or other court sports	Hours:	Minutes:	
32.	Basketball	Hours:	Minutes:	
33.	Football, soccer, or other field sports	Hours:	Minutes:	
34.	Skiing	Hours:	Minutes:	
35.	Bowling	Hours:	Minutes:	
Othe	rs (write in the name of activity):			
36.	Name of activity	Hours:	Minutes:	
37.	Name of activity	Hours:	Minutes:	
38.	Name of activity	Hours:	Minutes:	
39.	Today's date:			

Thank you for completing this survey. Please bring this completed survey with you to your scheduled PIVENS study visit.

PIVENS

PE - Physical Examination

Purpose: Record detailed physical exam findings.

When: Visits s1, f024, f048, and f096.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist, hip, and skin fold measurements are found in PIVENS SOP, Part I. In brief: Height, weight, waist and hips all should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other. Triceps skinfold measurements should be done on the right arm, with the elbow extended and the arm relaxed. Repeat skin fold measurements until you have two measurements within 10 mm of each other. Repeat mid-upper arm circumference measurements until you have two measurements within 1.5 in (3.8 cm) of each other.

A. Center, patient, and visit	identif	ication		9. Weight (shoes off)	
1. Center ID:				a. Weight, 1st measu	rement:
2. Patient ID:				b. Weight, 2nd measu	urement:
3. Patient code:	-			-	
				c. Units:	
4. Visit date:				Pounds	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
				Kilograms	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
day	mon		year		
5. Visit code:				of iliac crest and lo repeat waist measur	dpoint between highest point west part of costal margin; ements until you have two 4 in (10.2 cm) of each other)
6. Form & revision:	-	<u>p</u>	e1_	a. Circumference, 1st	t measurement:
7. Study:		PIVE	ENS_2_	_	
					waist circumference
B. Measurements				b. Circumference, 2n	d measurement:
8. Height (shoes off)				_	waist circumference
a. 1st measurement:				c. Units:	
			•	Inches	$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$
b. 2nd measurement:			•	Centimeters	(₂)
c. Units:					
Inches			$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
Centimeters			$\begin{pmatrix} 2 \end{pmatrix}$		

11.	Hip (standing, at fullest part of the hip measurements until you have two n within 4 in (10.2 cm) of each other)		15. Resting radial pulse:beats/minu	ite
	a. Circumference, 1st measurement:		16. Respiratory rate: breaths/	 minute
	hip circum		C. Examination findings	
	b. Circumference, 2nd measurement	•	17. Skin:	
	hip circum	ference	Normal	(1)
	c. Units:		20.	
	Inches	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	Abnormal (2)
	Centimeters	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	18. Acanthosis nigricans (check only one):	
12.	Triceps (right arm, with elbow exten	ded and arm	Absent (not detectable on close inspection) (()
	relaxed; repeat skin fold measureme have two within 10 mm of each of mid-upper arm circumference until within 1.5 in (3.8 cm) of each other)	ents until you other; repeat	Present (clearly present on close inspection, not visible to casual observer, extent not measurable)	(1)
	a. Skin fold, 1st measurement:	•	Mild (limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth)	(₂)
	b. Skin fold, 2nd measurement:	· — —	Moderate (extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front)	(3)
	c. Mid-upper arm circumference, 1st measurement:	•	Severe (extending anteriorly, > 6 inches in breadth, visible from front)	(4)
	arm circ	rumference	19. Other skin abnormality (check all that apply,)
	d. Mid-upper arm circumference, 2n	d	a. Jaundice:	(1)
	measurement:	•	b. Palmar erythema:	()
	arm circ	rumference		(1/
	e. Units for arm circumference:		c. Spider angiomata:	(1)
	Inches Centimeters	$\begin{pmatrix} 1 \\ 1 \end{pmatrix}$	d. Other (specify):	(1)
13.	Temperature (oral)	(2)	e. None of the above:	(1)
	a. Degrees:	•	20. Head, eyes, ears, nose, throat: Normal	(1)
	b. Scale:		Normal	、 1/ ⊢
	Fahrenheit	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	Abnormal	(,)
	Centigrade	$\begin{pmatrix} & & & & & & \\ & & & & & & \\ & & & & & $		2)
14.	Blood pressure		21. Abnormality of the head, eyes, nose, throat <i>(check all that apply)</i>	
	a. Systolic:		a. Jaundice:	(₁)
		mmHg	b. Other (specify):	(1)
	b. Diastolic:	mmHg	specify	

\mathbf{r}	Neck	
LL.	NECK	

Normal	(1)
Abnormal	23

specify abnormality

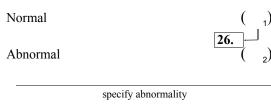
23. Lymphatic:



24. Chest and lungs:

Normal		(1)
Abnormal		25. (₂)
	specify adnormality	

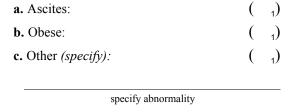
25. Heart:



26. Abdomen:



27. Abdomen abnormality *(check all that apply)*



28. Liver and spleen:

Normal	(1)
Abnormal	30.

29. Abnormality of liver or spleen (check all that ap-

a. Hepatomegaly (if checked,	y:		(1)
	span from	ı right	midclavicular
line):			
			•

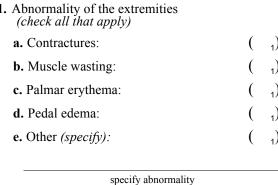
	cm		
b. Splenomegaly:		(1)
c. Other (specify):		(1)

specify abnormality

30. Extremities:

Not performed	()
Normal	32.
Abnormal	32.

31. Abnormality of the extremities



32. Genitourinary/pelvis:

Not performed	(0)
Normal	[33.]
Abnormal	(2)
specify a	abnormality

33. Nervous system:

Not performed (35.)

Abnormal



34. Abnormality of the nervous system *(check all that apply)*

a. Mental status abnormal:

b. Asterixis: (₁)

c. Other (specify):

specify abnormality

D. Administrative information

35. Study Physician PIN: ____ ____

36. Study Physician signature:

37. Clinical Coordinator PIN: ____ ___

38. Clinical Coordinator signature:

39. Date form reviewed:

day mon year

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.

When: Visits f004, f008, f016, f032, f064, f072, f080, and f120. Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurement are found in the PIVENS SOP Part I. In brief: height, weight, waist and hips should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

A. Center, patient, and visit id	lentification	9. Weight (shoes off)	
1. Center ID:		a. 1st measurement:	•
2. Patient ID:		b. 2nd measurement:	•
3. Patient code:		c. Units:	
		Pounds	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
4. Visit date:		Kilograms	$\begin{pmatrix} & & & & & & & & & & & & & & & & & & &$
	mon year	10. Waist (standing, at midpoint bet of iliac crest and lowest part repeat waist measurements within 4 in (10.2 cm) of each of	of costal margin; ntil you have two
6. Form & revision:	_pf1_	a. 1st measurement:	•
7. Study:	PIVENS 2	b. 2nd measurement:	•
B. Measurements		c. Units:	· —— ——
8. Height (shoes off)		Inches Centimeters	$\begin{pmatrix} & & & \\ & & 1 \end{pmatrix}$
a. 1st measurement:		11. Hip (standing, at fullest part of t measurements until you have tv (10.2 cm) of each other)	he hips; repeat hip wo within 4 in
b. 2nd measurement:		a. 1st measurement:	
c. Units:	(₁)	b. 2nd measurement:	<u> </u>
Centimeters	(2)	c. Units:	·
		Inches	()
		Centimeters	$\begin{pmatrix} 1 \\ 2 \end{pmatrix}$

year

12. Temperature (oral)	
a. Degrees:	
b. Scale: Fahrenheit: Centigrade:	(₁) (₂)
13. Blood pressure	
a. Systolic:	mmHg
b. Diastolic:	
14. Resting radial pulse:	beats/minute
15. Respiratory rate:	breaths/minute
C. Liver signs	
16. Liver and spleen:	
Normal	(1)
Abnormal	18. (₂)
17. Abnormality (check all that a	apply)
a. Ascites:	(1)
b. Asterixis:	(1)
c. Contractures:	(1)
d. Hepatomegaly:	(1)
If Yes, span from right mic	dclavicular line:
_	
e. Jaundice:	(1)
f. Muscle wasting:	(1)
g. Palmar erythema:	(1)
h. Pedal edema:	(1)
i. Spider angiomata:	(1)
j. Splenomegaly:	(1)

19. Study Physician signature:

21. Clinical Coordinator signature:

- **18.** Study Physician ID:
- **20.** Clinical Coordinator ID: ____ ___
- **22.** Date form reviewed:

A

QF - MOS 36-Item Short-Form Health Survey

Keyed: ()

Purpose: To obtain the patient's views of his/her health.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered, but Clinical Coordinator must be available at visits to answer questions and review the completed form.

Respondent: Patient, without help from spouse or family.

Instructions: The Clinical Coordinator should complete section A below and attach a label to each of pages 2-7.

Screening: The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-7. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-7 and the Clinical Coordinator should complete section B below. Followup: Pages 2-7 should be mailed to the patient 2 weeks prior to the scheduled study visit with instructions to complete the form at home and to bring the completed form to the next study visit. When the patient returns for the visit, the Clinical Coordinator should review the form for completeness and obtain responses for missing items during the visit. If the patient did not bring a completed form to the visit, the patient should complete the form at the visit. Page 1 should be attached to pages 2-7 and the Clinical Coordinator should complete section B below. Fill in item 4 with the date the patient wrote in item 22. If the patient did not write in a date, use the date of the study visit for the visit date.

. Ce	enter, visit, and patient i	dentification	(T	Iministrative information To be completed by Clinical Coordinator after	
1.	Center ID:		su	rvey is completed.)	
2.	Patient ID:		8.	Clinical Coordinator PIN:	_
3.	Patient code:		9.	Clinical Coordinator signature:	
4.	Date of visit (date patie	ent completed the form):			_
	day -	mon - year	10.	Date form reviewed:	
5.	Visit code:			day mon year	
6.	Form & revision:	<u>q</u> <u>f</u> <u>1</u>			
7	Study	DIVENS 2			

Affix label here
Patient ID:
Pt code:

QF - MOS 36-Item Short-Form Health Survey

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

(Items 1-10 are reserved for clinic use.)

11. In general, would you say your health is:

		Excellent	Circle	
		Very good		2
		Good		3
		Fair		4
		Poor		5
12.	Comp	pared to one year ago, how would you rate your health in general nov	v?	
		Much better now than one year ago		1
		Somewhat better now than one year ago		2
		About the same		3
		Somewhat worse now than one year ago		4
		Much worse now than one year ago		5

Affix label here
Patient ID:
Pt code:

13. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Circle one		
	Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports:	1	2	3
b.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:	1	2	3
c.	Lifting or carrying groceries:	1	2	3
d.	Climbing several flights of stairs:	1	2	3
e.	Climbing one flight of stairs:	1	2	3
f.	Bending, kneeling, or stooping:	1	2	3
g.	Walking more than a mile:	1	2	3
h.	Walking several blocks:	1	2	3
i.	Walking one block:	1	2	3
j.	Bathing or dressing yourself:	1	2	3

Affix l	abel here
Patient ID:	
Pt code:	
	ļ

14. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		Circle one	
		Yes	No
a.	Cut down on the amount of time you spent on work or other activities:	1	2
b.	Accomplished less than you would like:	1	2
c.	Were limited in the kind of work or other activities:	1	2
d.	Had difficulty performing the work or activities (for example, it took extra effort):	1	2

15. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		Circle one	
		Yes	No
a.	Cut down on the amount of time you spent on work or other activities:	1	2
b.	Accomplished less than you would like:	1	2
c.	Didn't do work or other activities as carefully as usual:	1	2

Affix label here
Patient ID:

16. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

	Not at all
	Slightly
	Moderately
	Quite a bit
	Extremely
17.	How much bodily pain have you had during the past 4 weeks?
	None
	Very mild
	Mild
	Moderate
	Severe
	Very severe
18.	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
	Not at all
	A little bit
	Moderately
	Quite a bit
	Extremely 5

Affix	label here
Patient ID:	
Pt code:	

19. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

		Circle one					
		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of pep?	1	2	3	4	5	6
b.	Have you been a very nervous person?	1	2	3	4	5	6
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d.	Have you felt calm and peaceful?	1	2	3	4	5	6
e.	Did you have a lot of energy?	1	2	3	4	5	6
f.	Have you felt downhearted and blue?	1	2	3	4	5	6
g.	Did you feel worn out?	1	2	3	4	5	6
h.	Have you been a happy person?	1	2	3	4	5	6
i.	Did you feel tired?	1	2	3	4	5	6

20. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Circl	e One
Most of the time		2
Some of the time		3
A little of the time		4
None of the time		5

Affix label here
Patient ID:

21. How TRUE or FALSE is *each* of the following statements for you.

		Circle one				
		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

22.	Date completed:		

 $\label{lem:please} \textbf{Please bring this completed survey with you to your scheduled PIVENS study visit.}$

RC - Rescreen in PIVENS

Purpose: To rescreen a patient who was previously found to be ineligible for PIVENS due to a temporary ineligibility. This form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 183-day screening window is reckoned from). The original RG form completed for the patient must remain in the data system. New screening phase tube and questionnaire labels will be available for printing upon keying this form.

When: Visit code s1.

Administered by: Clinical Coordinator.

Respondent: None.

Instructions: Complete this form for a patient who was previously found to be ineligible for PIVENS due to a temporary ineligibility and who now wants to rescreen for PIVENS. In general, the patient must complete all PIVENS screening data collection anew and all previously keyed PIVENS screening forms should be deleted from the data system except the RG and possibly the BC and CG forms. Update sections B, C, D, and G of the RG form and update the keyed record (you cannot delete the RG form). If blood was collected successfully for the Genetics Repository, a new sample does not need to be collected and the previously completed BC and CG forms may remain unchanged in the data system. Plasma and serum must be collected anew. If the same liver biopsy is being used to satisfy eligibility now and slides were sent to the DCC, additional slides do not need to be sent. The pathologist should rescore the biopsy and new SD, HF, and LT forms should be completed transcribing the slide numbers and liver tissue vial number as needed.

A. Center, patient, and visit identification		C. Administrative information			
1. Center ID:			9. Clinical Coordinator PIN:		
2. Patient ID:			10. Clinical Coordinator signature:		
3. Patient code:			; <u> </u>		
4. Date of visit:			11. Date form reviewed:		_
day	mon	year	day	mon	year
5. Visit code:	_S_		_		
6. Form & revision:		<u>r c 1</u>	-		
7. Study:		PIVENS 2	-		
B. PIVENS participation	1				
8. Date in item 4 of orig form:	inal PIVE	NS RG			
	mon		_		

RD – Study Drug Dispensing and Return

Keyed: (

Purpose: To record dispensing and return of study drugs.

When: Visits rz, f002, f004, f008, f012, f016, f024, f032, f040, f048, f056, f064, f072, f080, f088, and f096. Use visit code "n" if drugs are dispensed or returned at a time other than a regular study visit or if a second form is needed at a visit to document returned study drugs.

Administered by: Pharmacist or Clinical Coordinator, reviewed by Study Physician.

Instructions: This form documents dispensing of study drug, return of unused study drug, and return of empty study drug bottles. This form is required at visit rz and every scheduled followup visit thereafter except visit f120. It may be used at unscheduled visits as needed (use visit code n).

Study drugs are dispensed in the quantities specified below:

	No. of P series	No. of E series	
Visit	bottles	bottles	Comment
rz	1	1	4 week supply
f004	1	1	4 week supply
f008	1	1	8 week supply
f016	1	1	8 week supply
f024	1	1	8 week supply
f032	2	2	16 week supply
f048	2	2	16 week supply
f064	1	1	8 week supply
f072	1	1	8 week supply
f080	2	2	16 week supply

The patient should be queried about return of empty study drug bottles at all study visits. Unused study drug that has not expired should be returned to the patient for continued use. For expired study drugs that are returned, the pharmacist or the clinical coordinator should count and record the remaining number of tablets or softgels in study drug bottles. This form allows recording of the return of up to twelve bottles (six P series and six E series). If more than six bottles of either series are returned at a time, complete a second form (using visit code "n") to record the information for the remaining bottles.

A. Center, patient, and visit identification

4. Date of visit:

1.	Center ID:		 	
2.	Patient ID:			

- 3. Patient code:
- day mon
- 5. Visit code:
- d **6.** Form & revision: r
- 7. Study: PIVENS 2

B. Study drug dispensing

- **8.** Is this a second form for returning additional drug bottles at this visit:
- 9. Will study drug be dispensed today: No
- 10. Reason for not dispensing study drug (check all that apply)
 - Not a scheduled study drug dispensing visit:
 - Study physician-directed treatment interruption/termination:
 - Unwillingness of the participant to take study drugs:
 - **d.** Other (specify):

specify 18.

Patient ID:		

11. Number of P series bottles issued:

(1-2)

14. Number of E series bottles issued:

(1-2)

Bottle tear-off label

12.

Affix label here

13.

Affix label here

15.

Affix label here

Bottle tear-off label

16.

Affix label here

17. How were the study drugs dispensed to the patient *(check only one)*:

In person Mail

(₁)

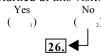
Other (specify)

(3)

specify

C. Study drug return

18. Were any P series bottles returned at this visit:



19. Number of P series bottles returned (if more than 6 bottles returned, complete a second RD form):

_			
	(1	-6)	

	a. Bottle No.	b. Number of tablets returned
20.	P	(00-50)
21.	P	(00-50)
22.	P	(00-50)
23.	P	 (00-50)
24.	P	(00-50)
25.	P	(00-50)

26. Were any E series bottles returned at this visit:



27. Number of E series bottles returned (if more than 6 bottles returned, complete a second RD form):

(1-6)

	a. Bottle No.	b. Number of softgels returned
28.	E	(00-50)
29.	E	(00-50)
30.	E	(00-50)
31.	E	(00-50)
32.	Е	

D. Remaining bottles

33.

34. Are any additional bottles being returned:

Yes	No
(* ₁)	(2)

(00-50)

(00-50)

*If yes, complete a second RD form using visit code "n."

E. Administrative information

2 =	Climinal C	:	DIM.	
J.D.	Clinical Co	orainator	PIN:	

36. Clinical Coordinator signature:

37. Date form reviewed:

	-	-	
day	mon	year	

PIVENS

RG - Registration

Purpose: To register patients as candidates for enrollment in PIVENS and to assign a patient ID number, if not already enrolled in a NASH CRN study. This is the first form completed for a PIVENS patient. The Registration Form must be the first form keyed, before any other PIVENS forms.

When: At first screening visit (s1). Administered by: Clinical Coordinator.

Respondent: Patient.

Instructions: Use Flash Cards as instructed. Do not assign a patient ID and code if patient has previously been as-

signed an ID for a NASH CRN study.

A	Conton	nationt	and	wigit	idan	tificat	ian
Α.	Center.	natient	and	VISIT	ıden	tificat	ıon

- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ __ ___
- **3.** Patient code: ____ ___
- 4. Visit date:

day	mon	year

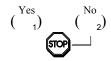
- **5.** Visit code: __s__1_______
- **6.** Form & revision: <u>r g 1</u>
- 7. Study: PIVENS 2

B. Consent

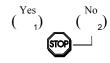
8. After reviewing the existing records (e.g., liver biopsy, elevated aminotransferases, and/or history) does the study physician feel that the patient may be suitable for the study:



9. Has the patient signed the PIVENS informed consent statement:



10. Has the consenter or study physician signed the consent form:



C. Information about patient

11. Date of birth:

=	·	
day	month	year
Record	4-digit year for day	te of hirth

- **12.** Age at last birthday:
- 13. Gender:

Male	(
Female	(;

14. Ethnic category (show the patient Flash Card #1 and ask the patient to pick the category that describes him/her best; check only one):

	16.
Not Hispanic, not Latino, not Latina	$\begin{pmatrix} 2 \end{pmatrix}$
Hispanic or Latino or Latina	$\begin{pmatrix} & & 1 \end{pmatrix}$

15. What describes your Hispanic, Latino, or Latina origin best (show the patient Flash Card #1 and ask the patient to pick the subcategory that best describes their Hispanic, Latino, or Latina origin; check only one):

Mexican (1)
Puerto Rican (2)
Cuban (3)
South or Central American (4)

Other Spanish culture or origin (5)

specify

16.	Racial category (show the patient Flash and ask the patient to pick the category or ries that describes him/her best; check apply) a. American Indian or Alaska Native:	r cate	ego- that	22. Which of the following categories best characterizes the patient's occupational history (show patient Flash Card #4 and patient to pick the category that describes best; check only one):		
		(1)	Never employed	(0
	b. Asian:	(1)	Laborer	(1)
	c. Black, African American, Negro, or	(`	Clerical	(2)
	Haitian:	(1)	Professional	(3)
	d. Native Hawaiian or other Pacific Islander:	()	Homemaker	(3) 4)
		(1)	Other, (specify):	(5)
	e. White:	(1)	outer, (speedyy).	(5)
	f. Patient refused:	(1)	specify		
17.	In what country was the patient born <i>(chone):</i> Continental US (includes Alaska) or	eck (,	23. Marital status of the patient (show patie Card #5 and ask the patient to pick the that describes him/her best; check only o	categ	lash gory
	Hawaii	(1)	Single, never married	(1)
	Other, (specify):	(2)	Married or living in marriage-like relationship	(2)
	specify			Separated, divorced, or annulled	(3)
				Widowed	(4)
18.	Highest educational level achieved by patient (show the patient Flash Card #3 the patient to pick the category that a him/her best; check only one): Never attended school			24. Combined annual income before taxes of all members of patient's household (show Flash Card #6 and ask the patient to category that describes his/her combine hold income best; check only one):	v pat pick	the
	Kindergarten, pre kindergarten, or	()	Less than \$15,000	(1)
	younger Grades 1 to 5	(1)	\$15,000 - \$29,999	(2)
	Grades 6-8	(2) 3)	\$30,000 - \$49,999	(3)
	Grades 9-11	(3) 4)	\$50,000 or more	(4)
	Completed high school	(`			
	Some college or post high school	(5)			
	education or training	(6)			
	Bachelor's degree or higher	(7)			
19.	Is the patient currently employed: $\binom{\mathrm{Yes}}{\mathrm{1}}$	(¹	No 2)			
20.	What is the patient's current occupation:					
	specify occupation					
21.	About how many hours does the patient work each week:	# hour				

D. Source of patient

(Clinical Coordinator should pick the best description of the source of patient)

25. Source of patient (check only one):

Bariatric surgery clinic	(01)
Current patient of NASH CRN investigator:	(02)
Diabetes clinic	(03)
GI/liver clinic	(04)
HMO-based	(05)
Internal medicine clinic	(06)
Lipid disorders clinic	(07)
Liver transplant clinic	((80
Obesity clinic	,	09)
Primary care clinic	(10)
Self referral	(11)
Other, (specify):	(12)

specify

E. Previous registration in a NASH CRN study

26. Has the patient previously been registered in a NASH CRN study:

27. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

specify		
b. Other, (spectyy).	(1.
b. Other, (specify):	(
a. NAFLD Database:	(1

- **28.** ID Number previously assigned to patient (record patient ID in item 2):
- 29. Code previously assigned to patient (record patient code in item 3):

30. Has it been at least 8 weeks since the patient was registered or enrolled in a NASH CRN study *(check only one)*:

Registered, but not enrolled

(* 0)

Yes

No

32.

(* 1)

32.

(* 2)

* Use physician discretion if less than 8 weeks since previous registration or enrollment.

F. ID assignment

(If a STOP condition was checked in section B, the patient is ineligible and a Patient ID should not be assigned. If the patient was previously registered in a NASH CRN study, a new ID number should not be assigned.)

31. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####, zzz

G. Administrative information

- **32.** Clinical Coordinator PIN: ____ ___
- **33.** Clinical Coordinator signature:
- 34. Date form reviewed:

 day mon year

PIVENS

SD - Liver Biopsy Materials Documentation

Purpose: To document that the liver biopsy required for screening was obtained under the time and medication restrictions required by the protocol and to document whether liver tissue was obtained for banking (both screening and followup biopsies). The number and type of slides available for archival at the Data Coordinating Center is noted for both screening and followup biopsies. If slides cannot be archived at the Data Coordinating Center, the source of the slides and the time by which the slides that must be returned to the clinical center are recorded.

When: Visits s1, f096, and as needed for biopsies at interim times.

By whom: Clinical Coordinator in consultation with the Study Pathologist.

Instructions: This form provides information about the tissue and slides from the biopsy and alerts the DCC to expect completion of the Liver Tissue Banking (LT) form, receipt of tissue at the Biosample Repository, and receipt of slides from the biopsy at the Data Coordinating Center. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and code, and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60, the borrowed slides should be labeled with removable overlabels with sequence numbers 81-90.

A. Center	. natient	and	visit	identification
-----------	-----------	-----	-------	----------------

- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- **4.** Date form initiated:

		_=
day	mon	year

- **5.** Visit code: ____ __ ___
- **6.** Form & revision: s d 2
- 7. Study: PIVENS 2

B. Surgical pathology report

8. Is a copy of the report annotated with the patient's NASH CRN ID number and code and with name blacked out attached to this form:



* Obtain a copy of the report, annotate it, and attach it. You can use one of the pathology labels to annotate the report.

9. Biopsy information

a. Date of biopsy specified on the surgical pathology report:

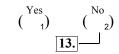
day	mon	year
obe specimen obto	ained from	

b. Lobe specimen obtained from *(check only one):*

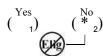
D: 14	(
Right	(1
Left	(2
Unknown	(2

C. Requirements for screening biopsy

10. Is this visit s1:

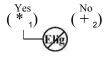


11. Is the date in item 9 within 6 months (183 days) of the anticipated date of randomization:



* Biopsy date must be within 6 months of randomization.

12. Were any proscribed medications (antiNASH medications or supplements, antidiabetic medications, antiobesity medications, or nonstable dose of fibrates or statins) used within 3 months of the date of the biopsy:



* Biopsy must be done when the patient has been free of proscribed medications (antiNASH medications or supplements, antidiabetic medications, and antiobesity medications) for at least 3 months prior to the date of the biopsy.

+ Since this is the screening biopsy, the local Study Pathologist must complete the Liver Biopsy Histology Findings (HF) form for this biopsy.

D. Biopsy specimens and stained slides at the clinical center

13. Was a sample of liver tissue obtained for banking:

 $\binom{\mathrm{Yes}}{*}_1$ $\binom{\mathrm{No}}{2}$ * If Yes, complete the Liver Tissue Banking (LT) form

14. What stained slides from the biopsy are available at the clinical center *(check all that apply)*

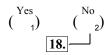
a. H & E stain: (______

b. Masson's trichrome stain: ()

c. Iron stain:

E. Unstained slides to be sent to the DCC

15. Are unstained slides available for sending to the DCC:



16. How many unstained slides will be sent to the DCC:

17. What are the slide sequence numbers for those slides (from the NASH CRN labels on each slide - use permanent labels, sequence numbers 01-60):

a. Slide sequence number

01-60

b. Slide sequence numberc. Slide sequence number

01-60

d. Slide sequence number

01-60

e. Slide sequence number

01-60

f. Slide sequence number

01-60

g. Slide sequence number

01-60

h. Slide sequence number

01-60

i. Slide sequence number

01-60

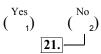
j. Slide sequence number

01-60

F. Stained slides to be sent to the DCC

(The institution's stained slides must be sent to the DCC only if fewer than 2 unstained slides will be sent to the DCC)

18. Is the institution's H & E stained slide to be sent to the DCC

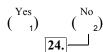


19. Slide sequence number for this slide (from the NASH CRN label on the slide - use removable overlabels, sequence numbers 81 - 90):

20. Is the H & E stained slide to be returned to the clinical center:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

21. Is the institution's Masson's trichrome stained slide to be sent to the DCC:



22. Slide sequence number for slide *(from the NASH CRN label on the slide - use removable overlabels, sequence numbers 81 - 90):*

(81-90)

23. Is the Masson's trichrome slide to be returned to the clinical center:

3	es .	N	lo
(1)	(2)

24. Is the institution's iron stained slide to be sent to the DCC:

(Y	res 1)	(No)
		27.	

25. Slide sequence number for the iron stained slide (from the NASH CRN label on the slide - use removable overlabels, sequence numbers 81 - 90):

(81-90)	

26. Is the iron stained slide to be returned to the clinical center:

Y	es	N	o
(1)	(2)

27. Is at least one of the stained slides to be returned to the clinical center (i.e., either item 20 = yes, item 23 = yes, or item 26 = yes):

(Y	es 1	(N	0
		30.	J

28. When do the stained slides need to returned to the clinical center (check only one):

Immediately after central review At the end of the NASH CRN funding

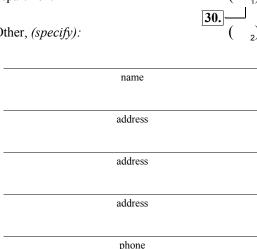
period

be	
11	

29. Which pathology department did these slides come from:

> NASH CRN clinical center's pathology department

Other,	(specify):
--------	------------



Note: this is the PIVENS trial record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

G. Administrative information

30. Clinical Coordinator PIN:

31.	Clinical Coordinator signature:	

32. Date form reviewed:

_		_
day	mon	year

PIVENS

Transfer Notification

Purpose: To record a transfer from one center to another center.

When: Upon transferring to the enrolling center and prior to the first visit at the adopting center.

By whom: Clinical coordinator of each center (enrolling center: sections A-C, adopting center: sections D- E).

Instruction: For enrolling center: When patient notifies enrolling center of upcoming transfer, the enrolling clinical coordinator should (1) complete Sections A-C of the Transfer Notification (TN Form), (2) send the TN form to the adopting center, with a copy of the most recently completed HI, LR, RD, and PE/PF forms, (3) send the labels for cryovials and slides and a copy of the visit window schedule to the adopting center. **For adopting center:** Prior to the patient coming to the adopting center, the adopting clinical coordinator should: (1) complete Sections D-E of the TN form, (2) Fax the TN form to the DCC (Fax: 410-955-0932). The DCC will key the form.

A. Enrolling center and patient identification	D. Adopting center, patient and visit identification			
1. Center ID:	14. Adopting center ID:			
2. Patient ID:	15. Patient ID (must be same as in Section A):			
3. Patient code:	16. Patient code: (must be same as in Section A):			
4. Date of notification of intent to transfer:				
day	17. Expected date of first followup visit at adopting center:			
	day mon year			
6. Form & revision: _t _ n _ 1 7. Study: PIVENS _2	18. Visit ID code for expected first followup visit at adopting center: f			
B. Last followup visit information				
8. Date of last followup visit:	Reminder: Please follow your local IRB require- ments regarding consent and HIPAA statements.			
day mon year	E. Adopting center administrative information			
9. Visit ID code of last completed followup visit: _f	19. Date form reviewed:			
10. Have cryovial and slide labels been sent to the adopting center: $ \begin{pmatrix} Yes & No \\ 1 & * \end{pmatrix} $	day mon year 20. Clinical coordinator ID:			
$\binom{1}{2}$ * Send the cryovial and slide labels to the adopting center.	21. Clinical coordinator signature:			
C. Enrolling center administrative information	Fax form to the DCC. The DCC will key the TN form.			
11. Date form reviewed:	<i>Je.m.</i>			
day mon year				
12. Clinical coordinator ID:				
13. Clinical coordinator signature:				

NASH CRN TONIC

TONIC Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
ВС	Blood Collection for DNA
BD	Food Questionnaire Documentation
BG	Baseline History
BP	Blood Processing for Plasma and Serum
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
DR	Death Report
DX	DEXA Scan for Body Fat
EC	Eligibility Checklist
FI	Family Member Identification
HI	Follow-up Medical History
ΙE	Interim Event Report
LP	Symptoms of Liver Disease (Children)
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LU	Laboratory Results - Tests Required at Visit s2
MA	Modifiable Activity Questionnaire
MR	MRI Report
MV	Missed or Incomplete Visit
PE	Physical Examination
PF	Focused Physical Examination
PQ	Pediatric QOL: Parent Report for Teens (Age 13-17)
PR	Pediatric QOL: Parent Report for Children (Age 8-12)
PW	Pediatric QOL: Child Report (Age 8-12)
PY	Pediatric QOL: Teen Report (Age 13-17)
RC	Rescreen Form
RD	Study Drug Dispensing and Return
RG	Registration
SD	Liver Biopsy Materials Documentation

TONIC

AD – Alcohol Use Disorders Identification Test (AUDIT)

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.

When: Visit s1.

Administered by: Self-administered (age 13 or older), interviewer administered (age 8-12). Clinical Coordinator must be available at visits to answer questions and review completed forms.

Respondent: Patient, age 8 or older. Patients age 13 or older should complete the form without help from family. Clinical Coordinator/parent can assist patients age 8-12.

Instructions: Flash Card #11, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator then should complete section B below.

A. Ce	enter, patient, and vi	sit identi	ficatio	n	В.			strative inform		2	
1.	Center ID:							s completed.)	inical Coordinator af	ier	
2.	Patient ID:					8.	How	was the questi	onnaire completed:		
3.	Patient code:						Self-	-administered b	y patient	(1)
4.	Date of visit (date p	oatient co	mpleted	d the form):					1	0.◀]
		mon		year				view in English view with trans		(₂) ₃)
5.	Visit code:	<u>s</u>	_1_			9.	Who	was the respon	ndent (check all that a	pply):	
6.	Form & revision:	-	a	<u>d</u>	<u>1</u>		a. b.		er or female guardian	(1) 1)
7.	Study:			TONIC	3		c. d.	Patient's fathe Other (specify	r or male guardian:):	(1) 1)
									specify		
						10.	Clina a. b.	ical Coordinato PIN: Signature:	r 		
						11.	Date	e form reviewed	:		
								day	mon	year	—

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below (*items 1-11 are for clinical center use only*).

12. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times a month	Two to three times a week	Four or more times a week
	(1)	(2)	(3)	(4)
<u> </u>				

13. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more
(0)	(1)	(2)	(3)	(4)

14. How often do you have six or more drinks on one occasion?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
(0)	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	(4)

15. How often during the last year have you found that you were not able to stop drinking once you had started?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$

16. How often during the last year have you failed to do what was normally expected from you because of drinking?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(1)	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	(4)

D. C. CID		
Patient ID:	 	

17. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 4 \end{pmatrix}$

18. How often during the last year have you had a feeling of guilt or remorse after drinking?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
(0	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

19. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

	Less than			Daily or	
Never	monthly	Monthly	Weekly	almost daily	
(0)	$\begin{pmatrix} & & 1 \end{pmatrix}$	$($ $_{2})$	$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$	

20. Have you or someone else been injured as a result of your drinking?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

21. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

22. Today's date:

Thank you for completing this questionnaire.

BC - Blood Collection for DNA

Purpose: Document the collection of whole blood for shipment to NIDDK Genetics Repository at Rutgers University for DNA extraction. Complete this form only if the patient signed the consent for genetic research.

When: Visit s2, rz, and as needed during followup. You can complete only one BC form prior to randomization. If a redraw of blood is necessary prior to randomization, revise the existing BC form to reflect the most recent blood draw for DNA banking. If redraw is necessary on the day of randomization, complete the BC form with visit code rz but hold the form for keying until after the patient has been randomized (you will not be able to key the form until after the patient has been randomized). If redraw is done after randomization or if the initial draw for DNA is done after randomization (eg, a patient who previously refused consent changes their mind to allow DNA banking), use the visit code for the followup visit whose time window is open. If redraw is done so soon after randomization that a followup visit window is not open, use visit code n.

By whom: Clinical Coordinator and laboratory personnel responsible for collection of whole blood.

Instructions: (1) Fill two 10 mL EDTA vacutainer tubes with whole blood. (2) Pack and ship the whole blood in the EDTA tubes to the NIDDK Genetics Repository at Rutgers University on the same day blood is collected. Ship at ambient room temperature. Ship whole blood in the specimen shippers supplied by the NIDDK Genetics Repository.

A. Center, patient and visit identification	C. Specimen for Genetics Repository			
1. Center ID:	Attach ID labels to two 10mL EDTA tubes and fill each with whole blood; invert each tube gently 6 times to mix blood with additives; keep tubes at			
2. Patient ID:	room temperature until the same day shipment to the NIDDK Genetics Repository.			
3. Patient code:	10. Was blood collected for the NIDDK Genetics Repository:			
4. Date of visit:	Yes (1)			
day mon year	No, (specify):			
5. Visit code:	specify			
6. Form & revision:bc1_	<u> 15.</u>			
7. Study: TONIC <u>3</u>	11. Date and time of blood draw a. Date:			
D. Cl. J.	day mon year			
B. Check on consent	b. Time:			
8. Did the patient/parent consent/assent to blood draw for DNA extraction:	hour minute (1) (2)			
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{*}_2$	12. Number of 10 mL EDTA tubes:			
(STOP)——	13. Form copy of tube labels:			
* You cannot proceed until you get consent.	TONIC Form BC			
9. Did the patient previously provide blood	Pt: ccc- 9999, xyz			
for DNA banking in the NAFLD	Gender			
Database:	Age, yrs.: XX			
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$				
15.	14. Phlebotomist:			
	print name			

D	Δ	dm	ini	ctra	tive	info	rme	ition
ν.	\boldsymbol{H}	uII	шш	SUI a	шус	HILLO	, , , , , ,	LLIVI

15. Clinical Coordinator PIN: ____ ___

16. Clinical Coordinator signature:

17. Date form reviewed:

day mon year

BD - Food Questionnaire Documentation

Purpose: To document completion of the age appropriate food questionnaire.

When: Visits s2, f048, f096, and f120. Administered by: Clinical Coordinator.

Instructions: Complete this form after the patient has completed the Block Brief Food Questionnaire. The Block Brief Food Questionnaire booklets should be sent to the DCC once a month with the completed TB form.

A. Center, patient, and visit identification			10. Form copy of label applied to food questionnaire:
1. Center ID:			г
2. Patient ID:	— — — —		TONIC Form BD
4. Date form completed (date food quest booklet is completed):	ionna	iire	C. Administrative information
day mon	year		11. Clinical Coordinator PIN:
5. Visit code:			12. Clinical Coordinator signature:
6. Form & revision:bc	<u>1</u>	<u></u>	
7. Study: TO	NIC	3	13. Date form reviewed:
B. Administration of food questionnaire			day mon year
8. How was the Brief Food Questionnaire completed:			
Self administered by patient/parent	(1)	
Interview in English	(2)	
Interview with translator	(3)	
9. Who was the respondent (check all that of	apply)		
a. Patient:	(1)	
b. Patient's mother or female guardian:	(1)	
c. Patient's father or male guardian:	(1)	
d. Other (specify):	(1)	
specify			

TONIC

BG - Baseline History

Purpose: To collect baseline history information about the patient.

When: Visit s1.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient or patient's parent.

Instructions: Collect information by interview or chart review. If \bigcirc is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for TONIC. If \bigcirc is checked for an item, the patient is ineligible and cannot enroll in TONIC. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

Α.	Center.	visit.	and	patient	identification	n
7 E.	Cuitti	V 15109	unu	patient	iuciitiitutioi	

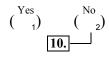
- **1.** Center ID: ____ ___
- **2.** Patient ID: ____ ___ ____
- 3. Patient code:
- **4.** Visit date (date this form is initiated):

		<u> </u>
day	mon	year

- **5.** Visit code: <u>s 1 ____ _</u>
- **6.** Form & revision: <u>b g 2</u>
- 7. Study: TONIC 3

B. Family history

8. Do any of the patient's first degree relatives (parent, brother, sister) have liver disease:

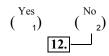


9. If yes, characterize the liver disease(s) *(check all that apply)*

a. Alcohol related liver disease:	(1))
--	---	----	---

specify

10. Do any of the patient's first degree relatives (parent, brother, sister) have cirrhosis:



11. If yes, is the cause of the cirrhosis unknown (cryptogenic):

12. Do any of the patient's first degree relatives (parent, brother, sister) have diabetes (Type 1 or Type 2):

13. Do any of the patient's first degree relatives (parent, brother, sister) have obesity:

14.	Do any of the patient's first degree			D. Weight history
	relatives (parent, brother, sister) have atrophy of body fat:			19. What was the patient's birthweight:
	Yes	(1)	<u> </u>
	No	(2)	lbs oz
	Don't know	(3)	20. What is the patient's current weight (ask the patient for his/her weight):
15.	Do any of the patient's first degree relatives (parent, brother, sister) have a problem with cholesterol or blood fat:			
	Yes	(1)	21. What is the most the patient has ever
	No	(2)	weighed:
	Don't know	(3)	
C N	AEI D.L.			lbs
	AFLD history Date patient was first diagnosed with			22. At what age did the patient weigh the most:
	nonalcoholic fatty liver disease (NAFLD):			age in years
	day mon	year		E. Tobacco cigarette smoking history (interview with patient; not by chart review)
17.	What prompted the evaluation for			· · · · · · · · · · · · · · · · · · ·
	NAFLD (check all that apply)			23. Have you ever smoked tobacco cigarettes:
	a. Symptoms for liver disease:	(1)	Never (
	b. Result of being evaluated for another			In the past but not anymore (28.
	illness:	(1)	Currently smokes cigarettes (3
	c. During a routine or insurance physical	(`	
	examination:	(1)	24. Did you smoke cigarettes regularly ("No" mean less than 20 packs of cigarettes in a lifetime or les
	d. Blood donation:	(1)	than 1 cigarette a day for one year):
	e. Other (specify):	(1)	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
	specify			20.
18.	What procedures/tests supported this first diagnosis (check all that apply)			25. How old were you when you first started regular cigarette smoking:
	a. Liver biopsy:	(1)	years
	b. Imaging studies (Ultrasound, CT, MRI)	: (1)	26. How old were you when you (last)
	c. Elevated aminotransferases:	(.)	stopped smoking cigarettes (code as ''n'' if the
	d. Other (specify):	(1)	patient didn't stop smoking):
	2. C	(17	years
	specify			years
				27. On the average of the entire time you smoked cigarettes, how many cigarettes did you smoke per day:

cigarettes/day

F. Menstrual history

28. Is the patient female:

$\binom{\text{Yes}}{1}$	$\binom{\text{No}}{2}$
	31.

- **29.** Menarche history
 - a. Has menarche occurred:

Yes	1)	(N	No 2
	31	l.	J

b. What was the patient's age at menarche:

	_	
age	in	years

30. Characterize the menstrual history in the past year (check only one):

Regular periods	(1
Irregular periods	(2
Rare periods	(3
No periods	(4

- G. Medical history (heart Caution; condition is exclusionary if study physician agrees with diagnosis)
- **31.** Has the patient ever been diagnosed with or treated for any of the following (check all that apply; source of information can be interview and/or chart review)
 - a. Diabetes type 1:



b. Diabetes type 2:



c. Gestational diabetes (diabetes of pregnancy):



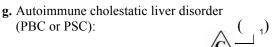
d. Hepatitis B:

^	(1)
$\langle \mathbf{c} \rangle$	_	
	•	

e. Hepatitis C:



f. Autoimmune hepatitis:



h. Wilson's disease:

(PBC or PSC):



i. Alpha-1-antitrypsin (A1AT) deficiency:



j. Hemochromatosis or iron overload:



k. Drug induced liver disease:



I. Gilbert's syndrome:



m. Esophageal or gastric varices on endoscopy:



n. Bleeding from varices:

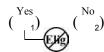


o. Other gastrointestinal bleeding:	(1)	al. Hyperlipidemia (high cholesterol, high triglycerides):	(1)
p. Biliary diversion:		am. Pancreatitis:	(1)
q. Metabolic acidosis:		an. Cholelithiasis:	(1)
r. Ascites:		ao. Coronary artery disease:	
s. Edema:	(₁)	ap. Congestive heart failure:	(₁)
t. Hepatic encephalopathy:	(₁)	aq. Elevated uric acid such as gout:	(1)
u. Portal hypertension:		ar. Kidney disease:	<u>(</u>)
v. Hanataranal aundrama:	()	as. Polycystic ovary syndrome:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
v. Hepatorenal syndrome:	<u>(c)</u>	at. Sleep apnea (not breathing during sleep):	(1)
w. Hepatopulmonary syndrome:	(1)	au. Dermatologic disorders:	(1)
	<u></u>	av. Myopathy:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
x. Short bowel syndrome:		aw. Myositis:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
	<u>C</u>	ax. Major depression:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
y. Hemophilia (bleeding disorder):		ay. Schizophrenia:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
	<u>/C\</u>	az. Bipolar disorder:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
z. Systemic autoimmune disorder suc rheumatoid arthritis or systemic lu		ba. Obsessive compulsive disorder:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
aa. Endocrine disease (hormonal abnormality):	(1)	bb. Severe anxiety or personality disorder:	(1)
ab. Hepatocellular carcinoma:	(1)	bc. Substance abuse:	<u>(</u>)
ac. Other malignancy (cancer):		bd. None of the above:	(1)
ad. Human immunodeficiency virus (HIV):	()	32. Has the patient ever had bariatric surg for any of the following <i>(check all the all the</i>	
(HIV).	<u>(</u>)	a. Stapling or banding of the stomach	
ae. Peripheral neuropathy:	(1)	b. Jejunoileal (or other intestinal)	
af. Seizure disorder or epilepsy:	(1)	bypass:	
ag. Drug allergies:	(1)		<u>C</u>
ah. Hypothyroidism:	(1)	c. Biliopancreatic diversion:	
ai. Hypertension:	(1)		<u>/C\</u>
aj. Cerebrovascular disease:	(1)	d. Other GI or bariatric surgery (spec	$(fy): \begin{pmatrix} 1 \end{pmatrix}$
ak. Dysbetalipoproteinemia:	(1)	e. None of the above:	

33. Is the patient currently undergoing evaluation for bariatric surgery:



34. Has the patient received total parenteral nutrition (TPN) in the past 3 years:



- 35. Organ, limb, or bone marrow transplant
 - **a.** Has the patient ever received a liver transplant:



b. Has the patient ever received any other organ, limb, or bone marrow transplant:



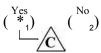
H. Drugs historically associated with NAFLD

36. Has the patient used any tetracyclines, salicylates, or valproic acid in the past 2 years (check all that apply)

a. Acetylsalicyl	ic acid (ASA):	(1)

-		
I. None of the above:	($\begin{pmatrix} 1 \end{pmatrix}$

37. Were any of the items in 36a-k checked:



*Caution: Use of any of these drugs for more than 2 consecutive weeks in the past 2 years is exclusionary.

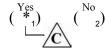
38. Has the patient taken any systemic corticosteroids in the past 2 years *(check all that apply):*

a. Betamethasone sodium (Celestone):

•	041	(:C.).	(`
J٠	Otner,	(specify):	(1

k. Other, (specify):	(4
no other, (speedy).	(- 1.

39. Were any of the items 38a-k checked:



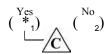
*Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past 2 years is exclusionary.

40.	Has the patient taken any anabolic		
	steroids or tamoxifen in the past 2 years		
	(check all that apply)		
	a Paldanana undaavlanata (Equinaiga)		

a.	Boldenone	undecylenate	(Equipoise):	$\begin{pmatrix} 1 \end{pmatrix}$

m. None of the above:
$$\begin{pmatrix} 1 \end{pmatrix}$$

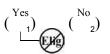
41. Were any of the items 40a-l checked:



*Caution: Use of anabolic steroids or tamoxifen for more than 2 consecutive weeks in the past 2 years is exclusionary.

I. Use of antidiabetic drugs

42. Does the patient have a known intolerance to metformin:



43.	Has the patient used any antidiabetic
	medications in the past 3 months
	(check all that apply):

a. Acarbose (Precose): (1.)
---------------------------------	----	---

n. Tolazamide (Tolinase):
$$\begin{pmatrix} 1 \end{pmatrix}$$

q. None of the above:
$$\begin{pmatrix} & & \\ & & \end{pmatrix}$$

44. Were any of the items 43a-p checked:



*Caution: Use of antidiabetic drugs in the 3 months prior to randomization is exclusionary.

J. Use of antiNAFLD drugs and vitamins

- **45.** Has the patient taken any of these antiNAFLD drugs in the past 3 months (check all that apply)
 - **a.** Betaine (Cystadone):
 - **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
 - **c.** Metformin:
 - **d.** Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol):
 - e. S-Adenylmethionine (SAM-e):
 - **f.** Milk thistle: (₁)
 - **g.** Probiotics (any form):
 - **h.** Gemfibrozil (Gen-Fibro, Lopid):
 - i. Other (specify):

specify

- **j.** None of the above: $\begin{pmatrix} 1 \end{pmatrix}$
- **46.** Were any of item 45a-h checked:

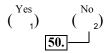


*Caution: Use of antiNAFLD drugs in the 3 months prior to randomization is exclusionary.

47. Has the patient taken a multivitamin regularly in the past 3 months:

$$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$$

48. Has the patient taken any vitamin E (either as a supplement or in a multivitamin) in the past 3 months:

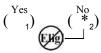


49. Was/Is the dose of vitamin E greater than 100 IU/day:



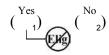
*Caution: Use of vitamin E at more than 100 IU/day in the 3 months prior to randomization is exclusionary.

50. Is the patient willing to refrain from taking vitamin E in amounts greater than 100 IU/day during TONIC:



*Patient may not take vitamin E supplements at doses greater than 100 IU/day during TONIC.

51. Does the patient have a known intolerance to vitamin E:



- **52.** What other vitamins (other than multivitamins and vitamin E) has the patient taken in the past 3 months *(check all that apply)*:
 - **a.** Vitamin B (any type):
 - **b.** Vitamin C:
 - **c.** Vitamin D:
 - **d.** Other, (specify):
 - e. None of the above: (1)

K. Use of statins, fibrates, and antiobesity drugs

- **53.** Has the patient taken any lipid lowering medications in the past 3 months *(check all that apply):*
 - **a.** Atorvastatin (Lipitor):
 - **b.** Colestipol hydrochloride (Colestid): (1)
 - **c.** Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate):
 - **d.** Fenofibrate (Tricor):
 - e. Fluvastatin sodium (Lescol):
 - **f.** Lovastatin (Mevacor):
 - g. Nicotinic acid (Niaspan): (1)
 - **h.** Pravastatin sodium (Pravachol): (1)
 - i. Rosuvastatin (Crestor):

 j. Simvastatin (Zocor):

 ()
 - **k.** Other, (specify):
 - **I.** None of the above:

54. Has the patient taken any antiobesity medications in the past 3 months			L. Use of other medications and supplements			
	(check all that apply): a. Dexfenfluramine hydrochloride (Redux):			56. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or		
			1)	aspirin containing medications in the past 3 months (check all that apply):		
	b. Fenfluramine hydrochloride (Pondimin):	(1)	a. Acetaminophen (Tylenol):	(1)
	c. Methamphetamine hydrochloride (Desoxyn, Gradumet):	(1)	b. Aspirin - 325 mg:c. Celecoxib (Celebrex):	(1) 1)
	d. Orlistat (Xenical):	(1)	d. Ibuprofen (Advil, Motrin):	(1)
	e. Phendimetrazine tartrate (Adipost,			e. Indomethacin (Indocin):	(1)
	Bontril):	(1)	f. Naproxen (Aleve, Naprosyn):	(1)
	f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):	(1)	g. Other, (specify):	(1)
	g. Sibutramine hydrochloride monohydrate (Meridia):	(1)	h. Other, (specify):	(1)
	h. Other, (specify):	(1)			17
	i. Other, (specify):	(1)	i. None of the above:	(1)
55	j. None of the above: Were any of the items 54a-i checked:	(1)	57. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 3 months <i>(check all that apply):</i>		
33.	Yes (*1)	. 1	No \	a. Cimetidine (Tagamet):	(1)
	(1)	7	2)	b. Esomeprazole magnesium (Nexium):	(1)
	*Caution: Use of antiobesity medications		he 3	c. Famotidine (Pepcid):	(1)
	months prior to randomization is exclusion			d. Lansoprazole (Prevacid):	(1)
				e. Nizatidine (Axid):	(1)
				f. Omeprazole (Prilosec):	(1)
				g. Ranitidine (Zantac):	(1)
				h. Ranitidine bismuth citrate (Tritec):	(1)
				i. Antacids, (specify):	(1)
				j. Other, (specify):	(1)
				k. Other, (specify):	(1)

I. None of the above:

asthma m that have	atient taken any allergy or redications in the past 3 months not already been reported on (check all that apply)		
a. Albute	erol:	(1)
	methasone dipropionate ovent, Vanceril):	(1)
c. Budeso	onide (Pulmicort, Rhinocort):	(1)
d. Flutica Flover	asone propionate (Flonase, at):	(1)
e. Lorata	dine (Claritin):	(1)
f. Momet	tasone furoate (Nasonex):	(1)
g. Triamo Nasaco	cinolone acetonide (Azmacort, ort):	(1)
h. Other,	(specify):	(1)
i. Other,	(specify):	(1)
j. None o	of the above:	(1)

59. Has the patient taken any supplements in the past 3 months that have not already been reported on this form <i>(check all that</i>	appl <u>:</u>	v)
a. Alpha-lipoic acid:	(1)
b. Beta-carotene:	(1)
c. Calcium (any form):	(1)
d. Carnitine (any form):	(1)
e. Chondroitin (any form):	(1)
f. Cod liver oil:	(1)
g. Coenzyme Q:	(1)
h. Dichloroacetate:	(1)
i. Echinacea:	(1)
j. Fish oil (any form):	(1)
k. Flax seed oil:	(1)
I. Garlic:	(1)
m. Ginkgo biloba:	(1)
n. Glucosamine (any form):	(1)
o. Lecithin:	(1)
p. Magnesium:	(1)
q. N-acetyl-cysteine:	(1)
r. Potassium (any form):	(1)
s. Saw palmetto:	(1)
t. Selenium:	(1)
u. St. John's Wort:	(1)
v. Taurine:	(1)
w. Zinc picolinate:	(1)
x. Other, (specify):	(1)

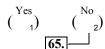
y. Other, (specify):

z. None of the above:

- **60.** Has patient taken any of the following medications in the past 3 months *(check all that apply)*
 - **a.** Isotretinoin (Accutane):
 - **b.** Levonorgestrel (Norplant):
 - **c.** Levothyroxine (Levoxyl, Synthroid): (
 - **d.** Liothyronine (Cytomel):
 - e. Oral contraceptives:
 - **f.** Penicillamine (Cuprimine, Depen): (1)
 - **g.** Trientine hydrochloride (Syprine): (1)
 - **h.** Other, (specify): $\begin{pmatrix} 1 \end{pmatrix}$
 - **i.** Other, (specify): $\begin{pmatrix} 1 \end{pmatrix}$
 - **j.** Other, (specify): $\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
 - **k.** Other, (specify):
 - l. Other, (specify):
 - m. None of the above:

M. Willingness to use effective birth control methods

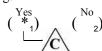
61. Are you female and of childbearing potential:



62. Are you currently pregnant:



63. Are you currently breast feeding:



*Caution: Patient cannot be breastfeeding at time of randomization.

64. Are you willing to use effective birth control methods during TONIC:



- N. Administrative information
- **65.** Study Physician PIN:
- **66.** Study Physician signature:
- **67.** Clinical Coordinator PIN:
- **68.** Clinical Coordinator signature:
- **69.** Date form reviewed:

_		_
day	mon	year

BP - Blood Processing for Plasma and Serum

Purpose: Document collection of fasting blood for local separation of plasma and serum and shipment to NIDDK Biosample Repository at Fisher BioServices.

When: Visits s2, f024, f048, f072, and f096.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of whole blood. **Instructions**: Put 2.7 mL of whole blood in CTAD tube and fill SST tubes with whole blood and prepare plasma and serum aliquots in the quantities specified below for the visit.

	Pla	Plasma:		ım:	
Visit	No. of CTAD tubes	No. of plasma aliquots	No. of 10 mL SST tubes to fill	No. of serum aliquots	
s2	1	2 or 3	4	40	
f024	none	none	2	20	
f048	1	2 or 3	4	40	
f072	none	none	2	20	
f096	1	2 or 3	4	40	

Label CTAD and SST tubes of whole blood using labels specific for the patient and visit; these labels are generated by the clinic upon registration (screening labels) or after randomization (followup visit labels). Attach duplicate whole blood tube labels in items 11 and 13 below. Process blood for plasma and serum within two hours. After separation, prepare 2 or 3 aliquots of plasma, depending on volume of plasma obtained: transfer 0.5 mL of plasma to each of 2 or 3 (2.0 mL) cryovials. After separation, transfer 0.5 mL of serum to each of the 20 or 40 (2.0 mL) cryovials depending on the visit. Label the plasma and serum cryovials with the numbered patient-specific plasma (blue top) and serum (red top) cryovial labels provided by the DCC. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Affix serum aliquot #00 label (all visits) and plasma aliquot #00 label (if visit s2, f048, or f096) to this form in item 18. The LS code keyed from the cryovial labels in item 18 of this form links the cryovials collected today with the date and visit identified in items 4 and 5 of this form. Freeze labeled aliquots of plasma and serum immediately according to procedures specified in the TONIC SOP, Part I. NOTE: Immediately upon completion of plasma and serum aliquot preparation, destroy any left-over cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be uniquely identified.

A. Center, patient and v	visit identification	6. Form & revision:	<u>b</u> p 1		
1. Center code:		7. Study:	TONIC_3_		
2. Patient ID:					
3. Patient code:					
4. Date of visit:					
day	mon year				
5. Visit code:					

Patient ID:		

B. Processing whole blood

Plasma and serum aliquots are to be separated from whole blood per instructions in the SOP. Draw fasting blood in the morning.

8. Was blood collected for the NIDDK Biosample Repository:

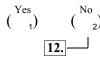
Yes	(1)
No, patient was not fasting for 12 hours	s (2)
No, other reason (specify):	23. (23. —	
specify other reason		

9. Date and time of blood draw

a.	Date:

_			
	day	mon	year
b. Time:			
	:	_ ((2
hour	minute	am	pm

10. Was blood collected for plasma banking at this visit (plasma banking is required at visits s2, f048, and f096):



11. Attach duplicate CTAD tube label:

	TONIC F	orm. BP, Plas.
	Pt:	9999, xyz
	Visit	vvvv
	Date:	
Į		

- **12.** Number of SST serum separator (red-top) tubes (4 tubes at visits s2, f048, and f096; 2 tubes at visits f024 and f072):
- **13.** Attach duplicate SST serum separator tube labels:

TONIC Serum 1
Pt: 9999, xyz
Visit: vvvv
BP
Date:

TONIC Serum 2
Pt: 9999, xyz
Visit: vvvv
BP
Date:

TONIC Serum 3
Pt: 9999, xyz
Visit: vvvv
BP
Date: ______

TONIC Serum 4
Pt: 9999, xyz
Visit: vvvv
BP
Date:

14. Phlebotomist:

print name	

C. Aliquots for plasma and serum

Pour 0.5 mL of plasma into each of up to three 2.0 mL pre-labeled cryovials and pour 0.5 mL of serum into each of forty 2.0 mL pre-labeled cryovials at visits s2, f048, and f096; 20 pre-labeled cryovials at visits f024 and f072.

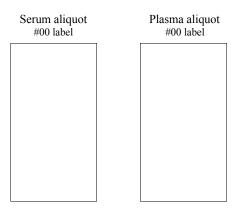
15. Date and time of separation into plasma and serum aliquots

a. Date:

	day	mon	year
b. Time:		,	
		- (1) (2)
hour	minute	am	pm

- **16.** Number of aliquots of plasma (if this was not a plasma banking visit, record "0"):
- **17.** Number of aliquots of serum:

18. Attach duplicate cryovial labels (use aliquot 00 labels which are located in the first row of labels for each label set):



19. Technician:

nrint name	

D. Freezing aliquots

Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK BioSample Repository at Fisher BioServices.

20. Date and time cryovials frozen in -70°C or -20°C

a. Date:			_=
	day	mon	year
h Time:			

- **21.** Number of cryovials frozen: _____
- 22. Technician:

 print name

E. Administrative information

- 23. Clinical Coordinator PIN: ____ ___
- **24.** Clinical Coordinator signature:
- 25. Date form reviewed:

 day mon year

TONIC

CG - Genetic Consent Documentation

Purpose: To document consent options selected for use of DNA samples for genetic research.

When: Visit s2 and as needed during followup (during followup, use the visit code of the followup visit that is

By whom: Study Physician and Clinical Coordinator.

Instructions: Complete this form based on the consent documents signed by the patient/parent. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG

A. Center, patient and visit identification	11. Other information related to consent for genetic research that clinic staff feel
1. Center ID:	needs to be keyed to the study database (e.g., if your genetic consent had other options that are not
2. Patient ID:	covered by the 3 categories of use of samples specified above):
3. Patient code:	
4. Date form completed:	
day mon year	-
5. Visit code:	
6. Form & revision: <u>c g 1</u>	 12. In your judgment, has the patient/parent consented to collection of blood for DNA banking (this question is asked in recognition that not all IRBs will have approved consent statements
7. Study: TONIC <u>3</u>	that include language that can be mapped into the questions in items 8 through 10; a response of "No" to this question (item 12) means that blood
B. Consent for collection, storage, and use of DNA samples for current and future genetic research	should <u>NOT</u> be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):
8. Does the patient/guardian consent to genetic research on NAFLD that is	$\begin{pmatrix} \text{Yes} & \begin{pmatrix} \text{No} \\ 1 \end{pmatrix} & \begin{pmatrix} \frac{\text{No}}{2} \end{pmatrix} \end{pmatrix}$
currently planned by the study investigators:	C. Administrative information
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{1}$	13. Study Physician PIN:
9. Does the patient/guardian consent to future genetic research on NAFLD by this study or other study investigators:	14. Study Physician signature:
Yes (No	2) 15. Clinical Coordinator PIN:
10. Does the patient/guardian consent to future genetic research on liver disease, its complications, and metabolic	16. Clinical Coordinator signature:
disorders by this study or other study investigators:	17. Date form reviewed:
	day mon year

CO - Closeout Form

Purpose: To close out a patient's participation in TONIC and document the patient's assent or consent or parental consent to join or re-enter the NAFLD Database.

When: At f120 visit or at the close of the f120 visit window.

Administered by: Clinical coordinator.

Respondent: None.

Instructions: Complete this form for each patient randomized in TONIC at the f120 visit or at the close of the f120 window. Determine if the patient now wants to re-enter or join the NAFLD Database. Schedule the patient for a NAFLD Database follow-up visit approximately 6 months from this visit.

- (1) Patients previously enrolled in the NAFLD Database: consult the NAFLD Database visit schedule generated at NAFLD enrollment and use the visit window that is open in 6 months (f144 or f192).
- (2) Patients NOT previously enrolled in the NAFLD Database: if patient is willing to join the NAFLD Database, a visit schedule will be generated upon keying this form. Schedule the participant approximately 6 months from their TONIC f120 visit for their f144 NAFLD Database follow-up visit.

A .	Cantar	natient	and	wieit	idan	tifica	tior

- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- 4. Date of visit:

_		
day	mon	year

- **5.** Visit code: <u>f 1 2 0</u>
- **7.** Study: TONIC <u>3</u>

B. Database participation

8. Does the patient wish to re-enter or join the NAFLD Database:

- **9.** Has the latest version of the NAFLD Database informed consent and/or assent been signed *(check all that apply)*
 - **a.** Consent signed by patient:
 - **b.** Assent signed by patient (must have guardian sign the consent): (
 - **c.** Consent signed by guardian:
 - **d.** No

10. Was the patient previously enrolled in the NAFLD Database:

Yes	No
(*)	(+)
(1/	(' 2

- * Schedule the patient's next NAFLD Database follow-up visit approximately 6 months from the date in item 4. Consult the patient's NAFLD Database visit window schedule and use the NAFLD Database visit open on that date.
- + Data system will generate a visit window schedule assigning the TONIC randomization date as the NAFLD Database enrollment date. Schedule the patient approximately 6 months from the date in item 4 for their f144 NAFLD Database followup visit.

C. Administrative information

- **11.** Clinical Coordinator PIN:
- **12.** Clinical Coordinator signature:
- **13.** Date form reviewed:



^{*} Informed consent must be signed

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee. By whom: Data Coordinating Center staff.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

	A. Clinic, patient and visit identification 1. Center ID
	2. Patient ID
	3. Patient code
///	4. Date of central reading
	5. Visit code
<u>c r 1</u>	6. Form and revision
	7. Study: 1 =Database; 2 =PIVENS; 3 =TONIC
///	8. Date of biopsy
	B. Slide sequence number9. Sequence number for a. H & E stained slide
	b. Masson's trichrome stained slide
	c. Iron stained slide
	d. Other slide
	Specify type of stain for other slide
	C. Administrative information 10. CC Initials
	11. CC Signature
///////	12. Date form reviewed
_	13. Tissue adequate: 0 =No → Request original slides from submitting clinic; 1 =Yes
	14. Followup with clinic (Specify):

Patient ID	D. Histology	
15. Biopsy length (mm)		
H & E stain		
	e.g., large and small droplet)	
a. Grade: 0 =<5%; 1 =5-33		
The state of the s	central); 1=Zone 1 (periportal); 2=Azonal; 3=Panacinar	
c. Microvesicular steatos	sis, contiguous patches: 0 =Absent; 1 =Present	
17. Inflammation		
a. Amount of lobular infl	lammation: combines mononuclear, fat granulomas, and pmn foci:	
	x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag	
b. Microgranulomas seen		
c. Large lipogranulomas		
d. Amount of portal, chro	onic inflammation: 0 =None; 1 =Mild; 2 =More than mild	
18. Liver cell injury		
a. Ballooning: 0 =None; 1		
b. Acidophil bodies: 0 =R	· •	
	es (Kupffer cells): 0 =Rare/absent; 1 =Many	
d. Megamitochondria: 0 =	=Rare/absent; 1=Many	
19. Mallory's hyaline: 0 =Rar	re/absent; 1=Many	
20. Glycogen nuclei: 0 =Rare	/absent; 1=Many	
Masson's trichrome stain		
	1a=Mild, zone 3 perisinusoidal (requires trichrome);	
	erisinusoidal (does not require trichrome); 1c=Portal/periportal only;	
2 =Zone 3 and periportal,	any combination; 3 =Bridging; 4 =Cirrhosis	
22. Iron stain		
a. Hepatocellular iron gra	ade: 0=Absent or barely discernible, 40x → GOTO item 22c;	
1=Barely discernable	e granules, 20x; 2 =Discrete granules resolved, 10x; 3 =Discrete granules resolved,	4x;
4 =Masses visible by	·	
	stribution: 0 =Periportal; 1 =Periportal and midzonal; 2 =Panacinar; 3 =Zone 3 or azo	onal
	n grade: 0=None → GOTO item 23; 1=Mild; 2=More than mild	
	n distribution: 0=Large vessel endothelium only; 1=Portal/fibrosis bands only, but	more
than just in large ves	sel endothelium; 2 =Intraparenchymal only; 3 =Both portal and intraparenchymal	
23. Is this steatohepatitis? 0 =	No; 1a=Suspicious/borderline/indeterminate: Zone 3 pattern;	
1b=Suspicious/borderline	e/indeterminate: Zone 1, periportal pattern; 2 =Yes, definite	
24. Is cirrhosis present? 0 =No	o → GOTO item 27; 1=Yes	
25. Is this cryptogenic cirrho	sis: 0 =No → GOTO item 27 ; 1 =Yes	
26. Features suggestive of ste	eatohepatitis etiology for cryptogenic cirrhosis:	
	e out cholate stasis): 0 =Absent; 1 =Present	
	away from septa: 0 =Absent; 1 =Present	
c. Hepatocyte ballooning	· · · · · · · · · · · · · · · · · · ·	
d. Megamitochondria: 0 =		
e. Other notable findings	: 0 =Absent; 1 =Present; Specify:	
27. Other comments:		

DR - Death Report

Purpose: To record the report of a patient's death.

When: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete this form whenever the clinical center is informed of a patient's death. If the death is considered associated or possibly associated with participation in TONIC, complete a Serious Adverse Event (AN) form and follow the directions on Form AN for reporting a SAE in TONIC.

A. Center, patient, and visi	t identifi	cation		10. Place of death:	
1. Center ID:				city/state/country	_
2. Patient ID:				city/state/country	
3. Patient code:4. Date form is initiated (d.	ate of not			11. Cause of death (Study Physician: use whatever knowledge yo have and your best medical judgment to best cha acterize the cause of death; check only one):	วน :r-
	mon				1)
day	Шоп	year			2)
5. Visit code:	_n				3)
				Malignancy (4)
6. Form & revision:	-	_dr	1_	Other (specify):	₅)
7. Study:		TONIC_	3	specify	_
B. Death information				specify	_
8. Date of death:				Unknown (6)
	mon	year		C. Administrative information	
9. Source of death report (a)	check all	that apply):		12. Study Physician PIN:	_
a. Patient's family:		(1)		
b. Friend:		(1)	13. Study Physician signature:	
c. Health care provider staff:	or NASH	CRN (1)	14. Clinical Coordinator PIN:	_
d. Newspaper:		(1)	14. Chinear Coordinator I IIV.	_
e. Funeral parlor/home:		(1)	15. Clinical Coordinator signature:	
f. Medical record:		(1)		
g. Medical examiner:		(1)	16. Date form reviewed:	
h. Coroner:		(1)	To. Date form reviewed.	
i. Other (specify):		(1)	day mon year	
othe	er source				
othe	er source				

DX - DEXA Scan for Body Fat

Purpose: To record DEXA scan measurements.

When: Visits s2 and f096.

Administered by: Clinical coordinator.

Instructions: A DEXA scan done in the year prior to starting screening for TONIC or during screening for TONIC may be used as the visit s2 DEXA scan. Transfer the DEXA scan measures from your institutional report to Section C. Attach a copy of the original DEXA report to this form.

A. Center, patient, and visit iden	tification	1	10. DEXA scanner used:	
1. Center ID:			Hologic QDR 4500A Hologic QDR 4500W	$\begin{pmatrix} & & & \\ & & 1 \end{pmatrix}$
2. Patient ID:			Hologic New Discovery Series 1 Hologic Delphi QDR Series	
3. Patient code:			Hologic Delphi W Lunar Prodigy	$\begin{pmatrix} & & & & & & & & & & & & & & & & & & &$
4. Date of visit:			Other (specify)	(7)
day mo	n	year	specify make & mo	odel
5. Visit code:			C. DEXA results summary	
6. Form & revision:	_d	<u>x</u> _1_	11. Date of DEXA scan:	
7. Study:	T	ONIC 3	day mon	year
B. DEXA scan information			12. Trunk % fat (if your scanner repert fat and region % fat, record regreport):	orts both tissue % zion % fat on this
8. Did the patient have a whole lenergy x-ray absorptiometry (scan:		1		<u> </u>
10	Yes (1)	(No 2)	13. Total % fat (if your scanner report fat and region % fat, record regreport):	orts both tissue % zion % fat on this
9. Specify why DEXA scan was performed	not			•
a. Patient is too heavy:		(1)	C. Administrative information	
b. Scanner is broken:		(1)	14. Clinical Coordinator PIN:	
c. Other (specify):		(1)	15. Clinical Coordinator signature:	
specify				
		14.		
			16. Date form reviewed:	
			day mon	year

EC - Eligibility Checklist

Purpose: To check eligibility for TONIC with respect to items not checked elsewhere on TONIC screening forms and record reasons for ineligibility for patients found to be ineligible.

When: Visit rz.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: This form may be initiated at any time. If the patient proceeds to randomization, it must be reviewed on the day of randomization. Patients of childbearing potential must complete the randomization day pregnancy test at the clinic on the day of randomization. Patients who are not of childbearing potential may complete the randomization day visit over the telephone. If this is the case, these requirements must be followed:

- (1) If your consent statement has an area for affirmation of consent prior to randomization, the patient should have signed the affirmation at his/her last screening visit.
- (2) The clinical coordinator must confirm with the patient by telephone on the day of randomization, that the patient feels well and continues to consent to randomization.
- (3) The assigned study medication must be mailed to the patient on the day of randomization for delivery the next day.
- (4) The patient should be instructed to start the medications as soon as possible after receipt.

If w is checked for any item, complete the entire form, but note that the patient may not continue in the TONIC trial. If an item has not been assessed because the patient is ineligible, write "m" (missing) next to that item. This form should be completed for each patient for whom form RG was completed

A. Center, patient, visit, and study identification

1.	Center ID:		 	

2. Patient ID:	 	



4.	Visit	date	(date	this	form	is	initiated).	,

day	mon	year

5. Visit code: <u>r</u> <u>z</u>	
---	--

B. Alcohol use exclusion

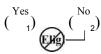
8. Does the patient have a history of significant alcohol intake:



9. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient (or the patient's parent/guardian) reliably quantify the child's *(past and current)* alcohol intake:

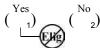


10. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient's alcohol use since starting the screening process consistent with TONIC eligibility criteria:



C. Cirrhosis exclusion

- 11. Clinical cirrhosis evaluation
 - **a.** Does the patient have varices or ascites <u>and</u> does the Study Physician judge that the patient has cirrhosis:

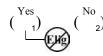


b. In the Study Physician's judgment, does the patient have cirrhosis (INR > 1.3, albumin < 3.0 g/dL, or conjugated bilirubin > 2 mg/dL may indicate cirrhosis):



D. Other chronic liver disease exclusions

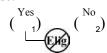
- 12. Evidence of autoimmune liver disease
 - a. Does the patient have ongoing autoimmune liver disease defined by the presence of anti-nuclear antibody (ANA) of greater than 1:80 and liver histology consistent with autoimmune liver disease:



b. In the Study Physician's judgment, does the patient have a history of autoimmune hepatitis:



13. Does the patient have Wilson's disease defined by the ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



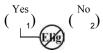
14. Does the patient have alpha-1 antitrypsin (A1AT) deficiency confirmed by A1AT level less than normal *(physician judgment)*:



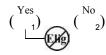
15. Does the patient have an iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:



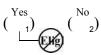
- **16.** Do any of the patient's assessments show evidence of other chronic liver disease
 - **a.** Drug induced liver disease as defined on the basis of typical exposure and history:



b. Known bile duct obstruction:

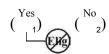


c. Any other type of liver disease other than NAFLD that warrants exclusion from the trial:

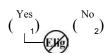


E. Other medical exclusions

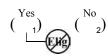
17. History of metabolic acidosis:



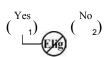
18. History of renal dysfunction:



19. History of coagulopathy:



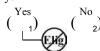
20. History of diabetes mellitus:



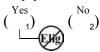
21. History of bariatric surgery (*jejunoileal bypass or gastric weight loss surgery*):



22. History of hepato-biliary surgery:



23. Inability to safely undergo liver biopsy:



24. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the 2 years prior to screening:



25. Use of antidiabetic drugs in the 3 months prior to randomization:



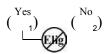
26. Use of antiNAFLD drugs in the 3 months prior to randomization:



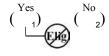
27. Use of antiobesity drugs in the 3 months prior to randomization:



28. Use of Vitamin E at a dose greater than 100 IU/day in the 3 months prior to randomization:



29. Known active, serious medical disease with a likely life-expectancy less than 5 years:



30. Known active substance abuse, such as alcohol or inhaled or injection drugs in the year prior to screening:



31. Other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study:



F. Birth control exclusion

32. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient willing to use effective birth control methods to avoid pregnancy during the 96 weeks of treatment:

Male or not of childbearing potential (0)
Yes (1)
No

G. Check on ability to swallow study medication

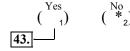
33. In your judgment (Study Physician/Clinical Coordinator), is the patient able to swallow the TONIC study medications (if you are unsure, you may ask the patient to swallow a capsule from the sample bottle of placebo metformin sent by the DCC prior to the start of TONIC):



H. Eligibility check on day of randomization

(Do in person if patient is of childbearing potential; otherwise, these checks may be done over the telephone with the patient <u>on the day of randomization.</u>)

34. Was an ineligibility condition checked or an eligibility not ascertained in items 8-33: Yes



*Key visits s1 and s2 forms RG, AD, BC, BD, BG, BP, CG, DX, HF, LP, LR, LS, LU, MA, MR (if available), PE, PQ/PR, PY/PW, SD. Run the Randomization Task on your clinic data system.

35. Were any stops or ineligible conditions other than "missing form EC" identified by the Randomization Task:

Yes

(1)

No

Task not run because patient is known to be ineligible

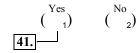
(3)

36. Does the patient feel well today:

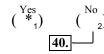


*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

37. Is the patient male:



38. Is the patient of childbearing potential:



*Administer pregnancy test.

39. Is the patient pregnant (positive pregnancy test on the day of randomization):



*Go to item 43.

40. Is the patient currently breast feeding:



*Go to item 43.

41. Per the Study Physician's judgment, is there any reason to exclude the patient from randomization:



*If Yes, specify reason and then go to item 43:

specify reason

42. Does the patient still consent to randomization (you should ask the patient to orally affirm his/her consent):



*Go to item 44 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.

†Complete items 43-48 and key the form. The form must be keyed to document the reasons for ineligibility for TONIC.

Note: Comple only.	ete this section for ineligible p	patie	ents
. Reason for in	eligibility (check all that app	ly)	
a. Reason co	vered in items 8-42:	(1)
b. Biopsy out chose not t	t of window and patient to repeat:	(1)
	dequate for scoring and use not to repeat:	(1)
d. Local path steatosis:	ologist did not find	(1)
	≥ 1.5 mg/dL for males or ≥ 1.4 mg/dL for females:	(1)
f. Positive for	r hepatitis B:	(1)
g. Positive fo	r hepatitis C:	(1)
h. ALT< 60 U	U/L:	(1)
i. ALT > 400	U/L:	(1)
-	um glucose ≥ 126 mg/dL or m glucose ≥ 200 mg/dL:	(1)
k. Known int	colerance to metformin:	(1)
I. Known into	olerance to vitamin E:	(1)
m. Liver tran	splant:	(1)
n. Currently surgery:	being evaluated for bariatric	(1)
o. TPN in the screening:	e past 3 years prior to	(1)
p. Inability to	swallow study medication:	(1)
-	outside time window and se not to repeat tests:	(1)
r. Other reason (specify):	on not covered on this form	(1)

J. Administrative information

- **44.** Study Physician PIN:
- **45.** Study Physician signature:
- **46.** Clinical Coordinator PIN: ____ ___
- **47.** Clinical Coordinator signature:

48. Date form reviewed

(Note re: patient proceeding to randomization: this form must be reviewed on the day of randomization; if it was keyed prior to the randomization day, update it and re-review it on the day of randomization and key the revised date of review.):

day	mon	year

(NOTE: If patient was not present in the clinic to receive the assigned medication, send the medication to the patient by overnight delivery service.)

FI - Family Member Identification

Purpose: To identify that a TONIC patient has one or more siblings (full, half or not biological) or parents (biological or not) enrolled in TONIC, PIVENS, or NAFLD Database.

When: As needed. Complete one FI form for each TONIC patient with siblings or parents enrolled in TONIC, PIVENS, or NAFLD Database. Update form as needed during follow-up if additional siblings or parents enroll in TONIC, PIVENS, or NAFLD Database.

By whom: Clinical coordinator.

Instructions: Form is to be completed if there is a patient randomized in TONIC who has one or more siblings or a parent enrolled in TONIC, PIVENS, or NAFLD Database. The index patient's study identifiers are recorded in section A. Up to 5 siblings can be entered on a form in section B. One mother and one father can be entered in section C. If there are more than 5 siblings (not including the index patient) or 1 of each parent in TONIC, PIVENS, or NAFLD Database, call the DCC for directions.

Please note: full and half siblings and biological parents do not need to live with the index patient. The not biological category would include non-blood related siblings or parents spending most of their time in the same household as the index patient, i.e., adoptive, step, foster, etc. Call the DCC with any questions.

A. Center, visit, and patient identification	9. First sibling
1. Center ID:	a. Patient ID:
2. Patient ID:	b. Patient code:
3. Patient code:	c. Biological relationship to index patient <i>(select one)</i> :
4. Date of visit:	Full (1)
	Half $\begin{pmatrix} & & \\ & 2 \end{pmatrix}$
day mon year	Not biological (3)
5. Visit code:n	Skip to item 14 if there are no more siblings enrolled in TONIC, PIVENS, or NAFLD Database.
6. Form & revision: <u>f i 1</u>	10. Second sibling
7. Study: TONIC <u>3</u>	a. Patient ID:
B. Study identifiers of sibling(s) of the index patient recorded in section A	b. Patient code:
8. How many siblings of the index patient	c. Biological relationship to index patient <i>(select one):</i>
identified in item 2 are enrolled in TONIC, PIVENS, or NAFLD Database	Full (1)
(if no siblings, code "0" and skip to item 14;	Half (2)
call the DCC if more than 5 siblings are enrolled in TONIC, PIVENS, or NAFLD	Not biological (3)
Database):	Skip to item 14 if there are no more siblings enrolled in TONIC, PIVENS, or NAFLD Database.
If zero (0), then skip to item 14	

11. Third sibling	C. Study identifiers of the parents of the index patient recorded in section A (call the DCC if
a. Patient ID:	more than 1 mother and/or 1 father are enrolled in PIVENS or NAFLD Database)
b. Patient code:	14. Mother of index patient
c. Biological relationship to index patient (select one): Full Half Not biological	a. Is the mother of the index patient enrolled in PIVENS or NAFLD Database: Yes No 15.
Skip to item 14 if there are no more siblings en rolled in TONIC, PIVENS, or NAFLD Database.	
12. Fourth sibling	c. Patient code:
a. Patient ID:	d. Biological relationship to index patient <i>(select one):</i>
b. Patient code:	Full $\begin{pmatrix} 1 \end{pmatrix}$ Not biological $\begin{pmatrix} 2 \end{pmatrix}$
c. Biological relationship to index patient <i>(select one):</i>	15. Father of index patient
Full Half Not biological (1 2	a. Is the father of the index patient enrolled in PIVENS or NAFLD Database: Yes No 2
Skip to item 14 if there are no more siblings en rolled in TONIC, PIVENS, or NAFLD Database.	- 16
13. Fifth sibling	b. Patient ID:
a. Patient ID:	c. Patient code:
b. Patient code:	d. Biological relationship to index patient (select one):
c. Biological relationship to index patient	Full (1)
(select one):	Not biological (2)
Full (1 Half) D. Administrative information
Not biological (3	16. Clinical coordinator PIN:
Call the DCC for instructions if there are mor siblings enrolled in TONIC, PIVENS, or NAFLI Database.	
	18. Date form reviewed:
	day mon year

HI - Followup Medical History

Purpose: To record followup medical history information about the patient.

When: Visits f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview or chart review.

A. Center, visit, and patient identification	D. Alcohol consumption (AUDIT-C) since the last visit (interview with patient)			
1. Center ID:	11. Since the last visit, how often have you had a drink containing alcohol:			
2. Patient ID:	Never (₀)			
3. Patient code:	14.			
	Monthly or less $\begin{pmatrix} 1 \end{pmatrix}$			
4. Visit date:	Two to four times a month (₂)			
	Two to three times a week $\binom{3}{3}$			
day mon year	Four or more times a week (4)			
5. Visit code:	12. Since the last visit, how many drinks containing alcohol did you have on a typical day when you are drinking:			
6. Form & revision: _h_i11	1 or 2 $\begin{pmatrix} 0 \end{pmatrix}$			
7 (4)	3 or 4			
7. Study: TONIC <u>3</u>	5 or 6 (₂)			
B. Interval identification	7 to 9 $\begin{pmatrix} 2 \\ 3 \end{pmatrix}$			
b. Interval identification	10 or more $\begin{pmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \end{pmatrix}$			
8. Date of last Followup Medical History form (if this is visit f004 then date of s1):	13. Since the last visit, how often have you had six or more drinks on one occasion:			
day mon year	Never (₀)			
	Less than monthly (1)			
9. Visit code of last Followup Medical	Monthly (2)			
History form (if this is visit f004 then s1):	Weekly (3)			
	Daily or almost daily			

C. NAFLD evaluation

10. Has the patient had a liver biopsy since the last visit:

 $\binom{\text{Yes}}{*}$ $\binom{\text{No}}{2}$

*Complete the Liver Biopsy Materials Documentation (SD) form.

ı		r. Ascites:	(1)
		s. Edema:	(1)
		t. Hepatic encephalopathy:	(1)
•		u. Portal hypertension:	(1)
(1	No \	v. Hepatorenal syndrome:	(1)
, 7]—	<i>2)</i> ⅃	w. Hepatopulmonary syndrome:		1)
<u>'•</u>		x. Short bowel syndrome:	(1)
		y. Hemophilia (bleeding disorder):	(1)
# (days	z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:	(1)
		<pre>aa. Endocrine disease (hormonal abnormality):</pre>	(1)
		ab. Hepatocellular carcinoma:	(1)
s per o	day	ac. Other malignancy (cancer):	(1)
		ad. Human immunodeficiency virus (HIV):	(1)
		ae. Peripheral neuropathy:	(1)
		af. Seizure disorder or epilepsy:	(1)
rt		ag. Drug allergies:	(1)
(1)	ah. Hypothyroidism:	(1)
(1)	ai. Hypertension:	(1)
		aj. Cerebrovascular disease:	(1)
(ak. Dysbetalipoproteinemia:	(1)
(1)	al. Hyperlipidemia (high cholesterol,	(`
(1)	,	(1) 1)
(1)		(
()		(1)
(• •	(1)
. (1)		(1)
. (1)		(1)
(•	(1)
((1)
(1)	sleep):	(1)
(1)	au. Dermatologic disorders:	(1)
(1)	av. Myopathy:	(1)
(1)	aw. Myositis:	(1)
(1)			
(1)			
		# days # days # t (1) (1) (1) (1) (1) (1) (1) (1) (1) (1	s. Edema: t. Hepatic encephalopathy: u. Portal hypertension: v. Hepatorenal syndrome: w. Hepatopulmonary syndrome: x. Short bowel syndrome: y. Hemophilia (bleeding disorder): z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: aa. Endocrine disease (hormonal abnormality): ab. Hepatocellular carcinoma: ac. Other malignancy (cancer): ad. Human immunodeficiency virus (HIV): ae. Peripheral neuropathy: af. Seizure disorder or epilepsy: ag. Drug allergies: (1) ah. Hypothyroidism: ai. Hypertension: aj. Cerebrovascular disease: (1) ak. Dysbetalipoproteinemia: al. Hyperlipidemia (high cholesterol, high triglycerides): am. Pancreatitis: an. Cholelithiasis: (1) ap. Congestive heart failure: aq. Elevated uric acid such as gout: (1) ar. Kidney disease: (1) ar. Kidney disease: (1) at. Sleep apnea (not breathing during sleep): (1) au. Dermatologic disorders: av. Myopathy: aw. Myositis: (1) aw. Myositis:	s. Edema: t. Hepatic encephalopathy: u. Portal hypertension: v. Hepatorenal syndrome: w. Hepatopulmonary syndrome: x. Short bowel syndrome: y. Hemophilia (bleeding disorder): aa. Endocrine disease (hormonal abnormality): ab. Hepatocellular carcinoma: ac. Other malignancy (cancer): ad. Human immunodeficiency virus (HIV): ae. Peripheral neuropathy: af. Seizure disorder or epilepsy: ag. Drug allergies: (1) ah. Hypothyroidism: (1) ai. Hypertension: aj. Cerebrovascular disease: (1) al. Hyperlipidemia (high cholesterol, high triglycerides): (1) an. Pancreatitis: an. Cholelithiasis: (1) ap. Congestive heart failure: (1) ap. Congestive heart failure: (1) ar. Kidney disease: (1) at. Sleep apnea (not breathing during sleep): (1) aw. Myopathy: (1) aw. Myositis: (1) aw. Myositis: (1) aw. Myositis: (1)

	ax. Major depression:	(1)	G. Medication use
	ay. Schizophrenia:	(1)	23. Since the last v
	az. Bipolar disorder:	(1)	any antidiabeti
	ba. Obsessive compulsive disorder:	(1)	(check all that
	bb. Severe anxiety or personality			a. Acarbose (F
	disorder:	(1)	b. Acetohexar
	bc. Substance abuse:	(1)	c. Chlorpropai
	bd. None of the above:	(1)	d. Glimepiride
4.0				e. Glipizide (C
18.	Since the last visit, has the patient had bariatric surgery for any of the following (check all that apply)			f. Glyburide (I Glynase):
	a. Stapling or banding of the stomach:	(1)	g. Insulin:
	b. Jejunoileal (or other intestinal) bypass:	(1)	h. Metformin
	c. Biliopancreatic diversion:	(1)	XR) (do no medication)
	d. Other GI or bariatric surgery, (specify):	(1)	i. Miglitol (Gl
		`	12	j. Nateglinide
	e. None of the above:	(1)	k. Pioglitazon
	0 1 0 1 0 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0	(17	I. Repaglinide
	Since the last visit, has the patient			m. Rosiglitazo
	received an organ, limb, or bone marrow transplant:			n. Tolazamide
	Yes	, N	lo /	o. Tolbutamid
	(1)	(2)	

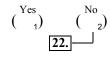
3.	Since the last visit, has the patient used any antidiabetic medications (check all that apply):		
	a. Acarbose (Precose):	(1)
	b. Acetohexamide (Dymelor):	(1)
	c. Chlorpropamide (Diabinese):	(1)
	d. Glimepiride (Amaryl):	(1)
	e. Glipizide (Glucotrol, Glucatrol XL):	(1)
	f. Glyburide (Micronase, DiaBeta, Glynase):	(1)
	g. Insulin:	(1)
	h. Metformin (Glucophage, Glucophage XR) (do not include TONIC study medication):	(1)
	i. Miglitol (Glycet):	(1))
	j. Nateglinide (Starlix):	(1)
	k. Pioglitazone (Actos):	(1)
	l. Repaglinide (Prandin):	(1)
	m. Rosiglitazone (Avandia):	(1)
	n. Tolazamide (Tolinase):	(1)
	o. Tolbutamide (Orinase):	(1)
	p. Other, (specify):	(1)

q. None of the above:

21. Since the last visit, has the patient been hospitalized:

received total parenteral nutrition (TPN):

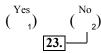
20. Since the last visit, has the patient



If Yes, specify reason:

specify

22. Since the last visit, has the patient had any serious health problem not already reported:



If Yes, specify:

specify

24.	Since the last visit, has the patient taken any lipid lowering medications (check all that apply):			26. Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing		
	a. Atorvastatin (Lipitor):	(1)	medications (check all that apply):	,	,
	b. Colestipol hydrochloride (Colestid):	(1)	a. Acetaminophen (Tylenol):	(1)
	c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate):	(1)	b. Aspirin - 325 mg:c. Celecoxib (Celebrex):	(1) 1)
	d. Gemfibrozil (Gen-Fibro, Lopid):	(1)	d. Ibuprofen (Advil, Motrin):	(1)
	e. Fenofibrate (Tricor):	(1)	e. Indomethacin (Indocin):	(1)
	f. Fluvastatin sodium (Lescol):	(1)	f. Naproxen (Aleve, Naprosyn):	(
	, , , ,	((1)
	g. Lovastatin (Mevacor):	(1)	g. Valdecoxib (Bextra):	(1)
	h. Nicotinic acid (Niaspan):	(1)	h. Other, (specify):	(1)
	i. Pravastatin sodium (Pravachol):	(1)			
	j. Rosuvastatin (Crestor):	(1)	i. Other, (specify):	(1)
	k. Simvastatin (Zocor):	(1)			
	l. Other, (specify):	(1)	j. None of the above:	(1)
25	m. None of the above:	(1)	27. Since the last visit, has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications		
25.	Since the last visit, has the patient taken any antiobesity medications (check all that	t app	ly):	(check all that apply):	(`
	a. Dexfenfluramine hydrochloride (Redux):b. Fenfluramine hydrochloride			a. Cimetidine (Tagamet):	(1)
		(1)	b. Esomeprazole magnesium (Nexium):	(1)
		(,	c. Famotidine (Pepcid):	(1)
	(Pondimin):	(1)	d. Lansoprazole (Prevacid):	(1)
	c. Methamphetamine hydrochloride (Desoxyn, Gradumet):	(1)	e. Nizatidine (Axid):	(1)
	d. Orlistat (Xenical):	(1)	f. Omeprazole (Prilosec):	(1)
	e. Phendimetrazine tartrate (Adipost,	(17	g. Ranitidine (Zantac):	(1)
	Bontril):	(1)	h. Ranitidine bismuth citrate (Tritec):	(1)
	f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):	(1)	i. Antacids, (specify):	(1)
	g. Sibutramine hydrochloride monohydrate (Meridia):	(1)	j. Other, (specify):	(1)
	h. Other, (specify):	(1)			
				k. Other, (specify):	(1)
	i. Other, (specify):	(1)			
				l. None of the above:	(1)
	j. None of the above:	(1)			

28.	Since the last visit, has the patient taken any systemic corticosteroids (check all that apply):		
	a. Betamethasone sodium (Celestone):	(1)
	b. Cortisol:	(1)
	c. Cortisone:	(1)
	d. Dexamethasone (Decadron):	(1)
	e. Hydrocortisone (Hydrocortone):	(1)
	f. Methylprednisolone (Solu-Medrol):	(1)
	g. Prednisolone (Prelone):	(1)
	h. Prednisone:	(1)
	i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort):	(1)
	j. Other, (specify):	(1)
	k. Other, (specify):	(1)
	l. None of the above:	(1)
29.	Since the last visit, has the patient taken any anabolic steroids or tamoxifen (check all that apply):		
	a. Boldenone undecylenate (Equipoise):	(1)
	b. Fluoxymesterone (Android-F, Halotestin):	(1)
	c. Methandrostenolone (Dianabol):	(1)
	d. Methyltestosterone (Android):	(1)
	e. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin):	(1)
	f. Oxandrolone (Oxandrin):	(1)
	g. Oxymetholone (Anadrol):	(1)
	h. Stanzolol (Winstrol):	(1)
	i. Tamoxifen (Nolvadex):	(1)
	j. Testosterone (Depo Testosterone):	(1)
	k. Other, (specify):	(1)
	l. Other, (specify):	(1)
	m. None of the above:	(1)

30.	Since the last visit, has the patient taken
	any allergy or asthma medications
	(check all that apply):

a. Albuterol:	(1)
b. Beclomethasone dipropionate (Beclovent, Vanceril):	(1)
c. Budesonide (Pulmicort, Rhinocort):	(1)

d. Fluticasone propionate (Flonase, Flovent):
$$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$$

g. Triamcinolone acetonide (Azmacort, Nasacort):
$$\binom{}{1}$$

i. Other, (specify):	(12
is other, (specify).	(17

j. None of the above:	(1
J	'	-12

31.	Since the last visit, has the patient taken a
	multivitamin regularly:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

32. Since the last visit, has the patient taken vitamins other than multivitamins (*do not include TONIC study medication*):

33. Which vitamins has the patient taken *(check all that apply):*

34. Is the patient currently taking vitamin E at a dose greater than 100 IU/day (do not include TONIC study medication):

$$\binom{\text{Yes}}{*}$$
 $\binom{\text{No}}{2}$

^{*}Remind patient not to take vitamin E supplements at doses greater than 100 IU/day during TONIC.

Since the lest visit has the resting to 1			26 Singa the last visit has the nations to 1		
Since the last visit, has the patient taken any supplements (check all that apply):			36. Since the last visit, has the patient taken any of the following medications or other		
a. Alpha-lipoic acid:		1)	supplements or medications (record all oth plements or medications):	l other sup	
b. Beta-carotene:	(1)	a. Acetylsalicylic acid (ASA):	(1)
c. Betaine (Cystadane):	(1)	b. Aspirin - 325 mg:	(1)
d. Calcium (any form):	(1)	c. Demeclocycline (Declomycin):	(1)
e. Carnitine (any form):	(1)	d. Divalproex (Depakote):	(1)
f. Chondroitin (any form):	(1)	e. Doxycycline (Monodox):	(1)
g. Choline + methionine + betaine + adenosine + pyridoxine (Epocler):	(1)	f. Isotretinoin (Accutane):	(1)
h. Cod liver oil:	(1)	g. Levonorgestrel (Norplant):	(1)
i. Coenzyme Q:	(1)	h. Levothyroxine (Levoxyl, Synthroid):	(1)
j. Dichloroacetate:	(1)	i. Liothyronine (Cytomel):	(1)
k. Echinacea:	(1)	j. Minocycline (Dynacin, Minocin):	(1)
I. Fish oil (any form):	(1)	k. Oral contraceptives:	(1)
m. Flax seed oil:	(1)	I. Oxytetracycline (Terramycin):	(1)
n. Garlie:	(m. Penicillamine (Cuprimine, Depen):	(1)
o. Ginkgo biloba:	(1)	n. Tetracycline (Achromycin):	(1)
p. Glucosamine (any form):	(1)	o. Trientine hydrochloride (Syprine):	(1)
q. Lecithin:	(1) 1)	p. Ursodeoxycholic acid (Actigall, Urso, Ursodiol):	(1)
r. Magnesium:	(1)	q. Valproate sodium (Depacon):	(1)
s. Milk thistle:	(1)	r. Valproic acid (Depakene):	(1)
t. N-acetyl-cysteine:	(1)	s. Other, (specify):	(1)
u. Potassium (any form):	(1)	, (1 32)		12
v. Probiotics (any form):	(1)	t. Other, (specify):	()
w. S-adenylmethionine (SAM-e):	(1)	Guer, (speedy).	(1)
x. Saw palmetto:	(1)	n Other (anaifil)	(`
y. Selenium:	(1)	u. Other, (specify):	(1)
z. St. John's Wort:	(1)	01 ('C)		
aa. Taurine:	(1)	v. Other, (specify):	(1)
ab. Zinc picolinate:	(1)			
ac. Other, (specify):	(1)	w. Other, (specify):	(1)
ad. Other, (specify):	(1)	x. None of the above:	(1)
as None of the above:	(

D TD		
Patient ID:	 	

H. Administrative information

day

37.	Study Physician PIN:	 	
38.	Study Physician signature:		
39.	Clinical Coordinator PIN:	 	
40.	Clinical Coordinator signature:		
41.	Date form reviewed:		

mon

year

IE - Interim Event Report

Purpose: To document (1) events that occur after registration but before randomization, or between regular followup visits that impact on the patient's treatment or participation in TONIC (eg, temporary or permanent cessation of study medication), or (2) adverse events associated with study drug that do not meet the criteria for Serious Adverse Event/IND Safety Report (AN) form, or participation in TONIC, or (3) other event that clinical center staff feel should be reported now rather than wait until the next followup visit and that is not recorded on another TONIC form. Adverse events associated with TONIC study drugs that are both serious and unexpected should not be reported on this (IE) form, but should be recorded on the AN form.

When: As needed; use visit code n. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code n for first event, n1 for second event, etc.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 21) and the severity code (item 22) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Documents and then click on General Documents. Fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher (Fax 410-955-0932).

NASH CRN Data Coordinating Center telephone number: (410) 955-8175.

A. Center, patient, and vi	sit identificat	ion	C. Patient information	
1. Center ID:			9. Date randomized in TONIC not yet randomized):	(enter n if patient is
2. Patient ID:				on year
3. Patient code:			10. Gender:	,
4. Date of report:			Male	(1)
		=	Female	(2)
day	mon	year	11. Age at time of event:	years
5. Visit code:	<u>n</u>			•
6. Form & revision:	_i_	e1_	12. Is the patient currently receiv metformin-series study drug:	
				$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
7. Study:		TONIC 3	13. Is the patient currently receiv	
B. Visit interval identifica	ition		vitamin E-series study drug:	Ves No
8. Most recently complete	ted visit (scree	ening		$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
or followup)			14. Summarize the patient's histo treatment with TONIC study	drugs (eg, how long
a. Date: day	mon	year	has patient been on study dr any treatment interruptions):	
b. Visit code:				

D. Event description

15. Is the event associated with TONIC study drugs:

Y	es	N	Jo ر
(1)	(2)
	1	8.	J

16. Is the event due to the metformin-series study drug:

Definitely yes	(1)
Probably yes	(2)
Possibly yes	(3)
Probably no	(4)
Definitely no	(5)

17. Is the event due to the vitamin E-series study drug:

Definitely yes	(1)
Probably yes	(2)
Possibly yes	(3)
Probably no	(4)
Definitely no	(5)

18. Date event started:

day	mon	year

19. Nature of event (check all that apply)	19.	Nature	of event	(check all	that	apply)
---	-----	--------	----------	------------	------	--------

a. Drug dispensing mixup:	(1)
b. Medication related event:	(1)
c. Study procedure related event:	(1)
d. Drug interactions:	(1)
e. Worsening of a co-morbid illness:	(1)
f. Patient reported symptom of hepatotoxicity:	(1)
g. Hypoglycemia:	(1)
h. New-onset diabetes:	(1)
i. Pregnancy (patient):	(*1)
j. Intravenous contrast dye use:	(1)
k. General anesthesia:	(1)
l. Lactic acidosis:	(1)
m. Other (specify):	(1)

*TONIC study drugs will be discontinued if the patient herself is pregnant. Contact the NASH CRN Data Coordinating Center to unmask the study drugs. Complete a Study Drug Dispensing and Return (RD) Form.

711	I leceribe	avent.
4 U.	Describe	CVCIII.

21. Short name for event if applicable (short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents):

Not applicable	(0)

22. Severity grade (severity grades are list CTCAE v3.0 document avail www.nashcrn.com; click on Documents click on General Documents; use Seriou Event Report (AN) to report serious pected adverse events or call the DCC what to do):	lable at s and then us Adverse and unex-	E. Administrative inform26. Clinical Coordinator27. Clinical Coordinator
Not applicable	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	
Grade 1 - Mild	$\begin{pmatrix} 1 \end{pmatrix}$	
Grade 2 - Moderate	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	28. Study Physician PIN
Grade 3 - Severe	$\begin{pmatrix} & & \\ & & & \end{pmatrix}$	
Grade 4 - Life threatening or disabling	(4)	29. Study Physician sign
Grade 5 - Death	(*5)	
*Complete and key Death Report (DR)		
23. Date event resolved <i>(enter n if event resolved):</i>	is not yet	30. Date form reviewed: day
day mon 24. What action was taken:	year	Key this form and fa Ünalp-Arida) a copy is 3 or higher. We a
		reports on serious ev priate and timely stud reports will be revi Safety Officer, for a the Steering Committ toring Board.
25. Other comments on event:		toring Bouru.

١.			•	• .			• •	•		
	А	am	ıın	isti	rafi	ve :	ınt	ori	mati	on.
•				150		•		0.		011

26. Clinical Coordinator PIN:
27. Clinical Coordinator signature:
28. Study Physician PIN:
29. Study Physician signature:

this form and fax the DCC (Attention: Aynur lp-Arida) a copy of this form if severity grade or higher. We are asking for copies of these rts on serious events so that we assure approte and timely study wide review. The received rts will be reviewed by Jeanne Clark, the ty Officer for appropriate further review by ty Officer, for appropriate further review by teering Committee and Data and Safety Monig Board.

mon

year

A

LP - Symptoms of Liver Disease (Children)

Purpose:	To	obtain	the	patient's	view	of his/her	liver	disease	symptom s.
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When: Visits s2, f048, f096, and f120.

Administered by: Self-administered (age 13-17), interview er administered (age 8-12). Clinical Coordinator must be available to answer questions and review for completeness.

Respondent: Patient, age 8 through 17. Patient age 13 or older should complete the form without help from family. Clinical Coordinator/parent should assist patient age 8-12.

Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-4. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in the completion of the form, and then should complete pages 2-4. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should then complete section B below.

Ce	nter, patient, and vi	sit identific	cation	B. Administrative information (To be completed by Clinical Coordinator after				
1.	Center ID:			survey is complete	=	r ajter		
2.	Patient ID:			8. How was the	questionnaire completed	:		
3.	Patient code:			Self-adm inist	ered by patient/parent	(1)		
4.	Date of visit:					10. ◀		
	day -	mon	year	Interview in I		$\begin{pmatrix} & & 2 \\ & & 3 \end{pmatrix}$		
5.	Visit code:			9. Who was the	re sponde nt (check all the	at apply):		
6.	Form & revision:	_	<u>l p 1</u>	a. Patienb. Patier	nt: nt's mother or female	(1)		
7.	Study:		TONIC 3		ian: nt's father or male guardi (specify):	(
					specify			
				10. Clinical Coora. PIN:b. Signa				
				11. Date form rev	riewed:			
				day		year		

Affix label here
Patient ID:
Patient code:
Visit code:

Symptoms of Liver Disease

Instructions: People with liver disease may or may not have symptoms, such as pain over the liver area (under your ribs, right of your belly), feeling sick to your stomach, poor appetite (not feeling hungry), itching, or tiredness. In this questionnaire, we are trying to identify what symptoms you have, how severe they are, and how much they affect you.

(Items 1-11 are reserved for clinical center use.)

12. During the last month, how much have you been bothered by the following:

Circle one for each symptom

Degree of bother

	None at all	A little bit	Medium	Quite a bit	Extremely
a. Pain over liver (pain under ribs, right of your belly)	1	2	3	4	5
b . Nausea (sick to stomach)	1	2	3	4	5
c. Poor appetite (not hungry)	1	2	3	4	5
d. Fatigue (get tired easily)	1	2	3	4	5
e. Weight loss	1	2	3	4	5
f. Diarrhea (watery poop)	1	2	3	4	5
g. Muscle aches or cramps	1	2	3	4	5
h. Muscle weakness (feel limp)	1	2	3	4	5
i. Headaches	1	2	3	4	5
j. Easy bruising ("black and blue" marks are easy to get)	1	2	3	4	5
k. Itching	1	2	3	4	5
l. Irritability (get mad easily)	1	2	3	4	5
m. Depression/sadness	1	2	3	4	5
n. Trouble sleeping	1	2	3	4	5
o. Trouble concentrating (trouble with attention, thinking about one thing at a time)	1	2	3	4	5

Affix label here
Patient ID:
Patient code:
Visit code:

Circle one for each symptom

Degree of bother

	None at all	A little bit	Medium	Quite a bit	Extremely
p. Jaundice (yellow color to skin, eyes, etc)	1	2	3	4	5
q. Dark urine (dark pee)	1	2	3	4	5
r. Swelling of ankles	1	2	3	4	5
s. Swelling of abdomen (belly swells up)	1	2	3	4	5

13.	Which of the following best describes how tired you feel and how your tiredness affect
	you (choose only one):

Circle one

	(ircie on
	I feel normal and am not tired (If this is how you feel, please circle "1" and g to item number 17 – Thank you!)	
	I feel tired some of the time, but can do what I want to do without trouble I feel tired, and do what I want but with trouble	
	I feel tired and it keeps me from doing what I want to do	
14.	How often are you bothered by being tired (choose only one):	
	All day, every day	
	At least part of several days a week	
	At least part of one day a week	
	Not as much as above	. 5
15.	Are you tired (choose only one):	
	When you wake up in the morning	
	Or does it come on with the day	
	Or does it have no time pattern	. 3
16.	Do you feel more tired the day after you exercise or have a lot of activity:	
	Yes	. 1

Affix label here
Patient ID:
Patient code:
Visit code:

17. In general, how have you felt overall in the past month:

Very good	1
Good	2
Fair	3
Poor	4
Awful	5

18. Today's date:

Thank you for completing this questionnaire.

LR - Laboratory Results -Tests Done at Visit s1 and During Followup

Purpose: To record archival and current laboratory test results for tests done during both screening and followup. **When**: Visits s1, f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If is checked in item 63, the patient is not eligible for TONIC and the form should not be keyed. Attach copies of the laboratory reports to this form.

A. Center, patient, and visit identification	C. Hematology
1. Center ID:	Required at visits s1, f024, f048, f072, f096, and f120.
2. Patient ID:	11. Is hematology testing required at this visit:
3. Patient code:	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
4. Date of visit:	12. Date of blood draw for hematology:
day mon year	
5. Visit code:	day mon year Date must be within the required time window, within 3 months of screening or in the time window.
6. Form & revision:11	for the followup visit (check the patient's TONIC visit time window guide).
7. Study:	13. Hemoglobin:
TONIC 3	g/dL
B. Initial screening ALT	14. Hematocrit:
8. Is this visit s1:	70
$\binom{\operatorname{Yes}}{1}$ $\binom{\operatorname{No}}{2}$	15. White blood cell count (WBC):
11.	$10^3 \text{ cells/} \mu \text{L or } 10^9 \text{ cells/} \text{L}$
9. Date of blood draw for ALT (Date must be within 12 months of randomization and at least 30 days apart from the ALT done at the clinic for visit s2):	16. Platelet count:
	cells/ μL
day mon year	
10. Alanine aminotransferase (ALT) (if ALT ≤ 60 U/L, patient is ineligible; also, patient is ineligible if the ALT done closest in time to randomization is > 400 U/L):	
a. Upper limit of normal:	
b. Lower limit of normal:	

D. Metabolic panel

Required at all visits using the LR form (s1, f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120).

17. Date of blood draw for metabolic panel:

	<u>-</u>	
day	mon	year

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

1

 	_
mFa/L	

	•	
,	mEq/L	

	•	
-	mg/dL	

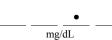
•	
 mg/dL	

mg	/dL

25. Creatinine (if serum creatinine ≥ 1.5 (1.4) mg/dL and patient is male (female), patient is ineligible):

•	
 mg/dL	_

26. Uric acid:



27. Albumin:

28. Total protein:

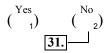


E. Fasting lipid profile

Required at visits s1, f024, f048, f072, f096, and f120.

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw.

29. Is fasting lipid profile required at this visit:



30. Date of blood draw for fasting lipid profile:

day	mon	year

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

a. Triglycerides:

mg/dL	
mg/ar	

b. Total cholesterol:

_		_
	mg/dL	

c. HDL cholesterol level:

mg/dL	

d. LDL cholesterol level:

	_
mg/dL	

F. Fasting glucose

Required at visits s1, f024, and f072. Also required at visits f048, f096, and f120 if the patient is diabetic.

Fasting is defined as nothing by mouth except water for at least 12 hours prior to blood draw.

31. Is fasting glucose required at this visit:

$$\begin{pmatrix}
Yes \\
1
\end{pmatrix} \qquad
\begin{pmatrix}
No \\
2
\end{pmatrix}$$
34.

32. Date of blood draw for fasting glucose level:

_		_
day	mon	year

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

33. Serum glucose (if fasting glucose 126 mg/dL or greater, patient is ineligible):

mg/dL	

G. Hepatic panel

Required at visits f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.

34. Is hepatic panel required at this visit:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	41.

35. Date of blood draw for hepatic panel:

•	oroou	aruw	101 110	patie p	unci.		
	d.					***	

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

- 36. Bilirubin (total):
- **37.** Bilirubin (conjugated or direct):

•	
 mg/dL	

38. Aspartate aminotransferase (AST)

 U/L	

- **a.** Upper limit of normal: U/L
- **b.** Lower limit of normal: U/L
- **39.** Alanine aminotransferase (ALT)

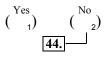
	U/L	

- **a.** Upper limit of normal: U/L
- **b.** Lower limit of normal: U/L
- 40. Alkaline phosphatase U/L
 - **a.** Upper limit of normal: U/L
 - **b.** Lower limit of normal: U/L

H. Vitamin B₁₂

Required at visits f024, f048, f072, f096, and f120.

41. Is vitamin B_{12} required at this visit:



42. Date of blood draw for vitamin B₁₂:

=		_
day	mon	year
e must be in the ti	me window for	the followu

Date visit (check the patient's TONIC visit time window guide).

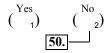
43. Vitamin B₁₂ (cobalamin) (if provided in pmol/L, multiply by 1.35 to convert to pg/ml):

	•
 pg/mL	

I. Prothrombin time, GGT, and HbA1c

Required at visits f048, f096, and f120.

44. Are the prothrombin time, GGT, and HbA1c tests required a this visit:



45. Date of blood draw for prothrombin time, GGT, and HbA1c:

day	mon	year
ate must be in the tin	ne window fo	r the followup
isit (check the natient		

guide).

- **46.** Prothrombin time (PT):
- **47.** International normalized ratio (INR):

	•	

48. Gamma glutamyl transferase (GGT):

	U/L	

49. HbA1c:

J. Oral glucose tolerance test

Required at visits f048, f096, and f120.

The oral glucose tolerance test will be performed. in the morning after a 12-hour overnight fasting. Baseline blood sample will be obtained for measurements of serum glucose, insulin, and C peptide. Blood sample will be obtained after 2 hours (120 minutes) for the measurement of serum glucose and insulin after oral administration of flavored glucose solution in a dose of 2 g/kg (75 g maximum).

50. Is oral glucose tolerance test (OGTT) required at this visit:

Yes	()
No	(2
No, patient is diabetic	54. (3
	54.

51. Date of blood draw for OGTT:

_		_
day	mon	year
D (1 : 1)	. 1 .	1 C 11

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

52. OGTT results at baseline

a. Serum glucose:	
C	mg/dL

- **b.** Serum insulin: $\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}$
- c. Serum C peptide:
- **53.** OGTT results at 2 hours

b. Serum insulin:	•
a. Serum glucose:	mg/dL
OOTT Tesuits at 2 Hours	

K. Free fatty acid, leptin, and C-reactive protein

Required at f048, f096, and f120.

54. Are free fatty acid, leptin, and C-reactive protein required at this visit:



55. Date of blood draw for free fatty acid, leptin and C-reactive protein (all serum):

		_=
day	mon	year
must be in the tin	ne window foi	r the followu

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

56. Free fatty acid:

μmol/L	

- **58.** C-reactive protein (if result is reported as normal but below your lab's detectable level, enter the cutoff for your lab's detectable level):

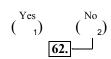
	•	
	mg/dL	

If units reported are mg/L, divide by 10 to convert to mg/dL.

L. Pregnancy test

Required at all study visits if applicable.

59. Is pregnancy test applicable:



60. Date of urine collection (or blood draw):

	`		
_		_	
 day	mon	vear	

Date must be the same day as date of visit.

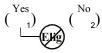
61. Pregnancy test results (*if pregnancy test is positive at s1, patient is ineligible*):

M. Eligibility check

62. Is this the s1 visit:



63. Was the patient found to be ineligible based on ALT (item 10), creatinine (item 25), fasting serum glucose (item 33), or pregnancy test (item 61):



- N. Administrative information
- **64.** Study Physician PIN:
- **65.** Study Physician signature:
- **66.** Clinical Coordinator PIN:
- **67.** Clinical Coordinator signature:
- **68.** Date form reviewed:

=		_	
day	mon		year

LS - Laboratory Results Tests Done Only During Screening

Purpose: To record archival and current results of laboratory tests done only at screening.

When: Visit s1.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. If is checked for any item the patient is not eligible for the TONIC trial. If ♠ is checked for an item, use caution. If the Study Physician agrees with the diagnosis, the patient is ineligible for TONIC.

A. Center, patient, and vi	sit identification	B. Screening etiologic tests
1. Center ID:		8. Date of blood draw for serological assays
2. Patient ID:		to exclude viral causes of chronic liver disease:
3. Patient code:		day mon year Repeat if date is greater than 1 year prior to screening.
4. Date of visit:		a. Hepatitis B surface antigen (HBsAg):
- Date of visit.	-	Positive
day	mon year	ENG-
5. Visit code:	s 1	Negative (2)
6. Form & revision:		b. Hepatitis B core total antibody (anti-HBc) (if total anti-HBc is not available, record results from IgG test):
7 (44	TONIC 3	Positive (1)
7. Study:	10111C_ <u>5</u> _	Negative (2)
		Not available (3)
		c. Hepatitis B surface antibody (anti-HBs):
		Positive (1)
		Negative (2)
		Not available $\begin{pmatrix} & & & \\ & & & \end{pmatrix}$
		d. Hepatitis C antibody (anti-HCV) (indicate result as negative if EIA is positive but RIBA is negative): Positive
		Negative (2)
		e. Hepatitis C virus RNA (HCV RNA):
		Positive (1)
		Negative (2)
		Not available (3)

C. Autoantibody studies

9. Date of blood draw for autoantibody tests:

day mon year

Repeat if date is greater than 5 years prior to screening.

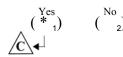
10. Antinuclear antibody (ANA):

Positive Negative (*₁) (₂)

a. If positive, ANA: 1/

* If results are given as units, record as "n" and key the actual result in the General Comments.

11. Is ANA titration greater than 1:80



* Check Liver Biopsy Histology Findings Form for autoimmune liver disease.

12. Antismooth muscle antibody (ASMA):

Positive Negative $\binom{*}{1}$

a. If positive, ASMA: 1/ ____ ___ ___

* If results are given as units, record as "n" and key the actual result in the General Comments.

13. Antimitochondrial antibody (AMA):

Positive Negative

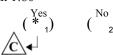
(* 1)

Not available



a. If positive, AMA: 1/ ____ __ ___

- * If results are given as units, record as "n" and key the actual result in the General Comments.
- 14. Is AMA titration greater than 1:80



* Check Liver Biopsy Histology Findings Form for primary biliary cirrhosis.

D. Ceruloplasmin

15. Date of blood draw for ceruloplasmin:

dav

mon year

Repeat if date is greater than 10 years prior to screening.

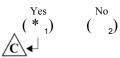
16. Ceruloplasmin

mg/dL

a. Lower limit of normal:

mg/dL

b. Is ceruloplasmin below the lower limit of normal:



* Check Liver Biopsy Histology Findings Form for Wilson's Disease.

E. Alpha-1 antitrypsin

17. Date of blood draw for alpha-1 antitrypsin (A1AT):

day mon

year

Repeat if date is greater than 10 years prior to screening.

18. Alpha-1 antitrypsin (A1AT)

mg/dL

a. Lower limit of normal:

mg/dL

b. A1AT deficiency (physician judgment):



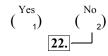
F. Iron

19. Date of blood draw for hemochromatosis screening:

mon

Repeat if date is greater than 5 years prior to screening.

- a. Iron: μg/dL
- **b.** Total Iron Binding Capacity: _
- **c.** Ferritin: ng/mL
- 20. Is hepatic iron index available:



21. Hepatic iron index: μmol/g/year

G. Administrative information

- 22. Study Physician PIN:
- **23.** Study Physician signature:
- 24. Clinic Coordinator PIN:
- **25.** Clinic Coordinator signature:
- **26.** Date form reviewed:

_		_
day	mon	vear

LU - Laboratory Results - Tests Required at Visit s2

Purpose: To record archival and current laboratory test results for tests required at visit s2.

When: Visit s2.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review except for hepatic panel which must be done at the TONIC clinical center on or after the date when screening started. Note that the ALT recorded for visit s1 and this hepatic panel (visit s2) must have been done at least 30 days apart. The hepatic panel done at visit s2 may pre-date the ALT recorded on the visit s1 LR form so long as the visit s2 hepatic panel is done on or after the date screening started. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If we is checked in any item, the patient is not eligible for TONIC and the form should not be keyed. Attach copies of the laboratory reports to this form.

A. Center, patient, and visit identification	11. Aspartate aminotransferase (AST)	
1. Center ID:		
2. Patient ID:	a. Upper limit of normal:	
3. Patient code:	b. Lower limit of normal:	
4. Date of visit:	U/L 12. Alanine aminotransferase (ALT) (if $ALT \le 60$ U/L,	
day mon year	patient is ineligible; patient is also ineligible if the ALT done closest in time to randomization is > 400 U/L)	
5. Visit code:		
6. Form & revision:	a. Upper limit of normal:	
7. Study: TONIC <u>3</u>	b. Lower limit of normal:	
B. Hepatic panel		
This hepatic panel must be done at TONIC clinical center on or after the date when screening started, and the ALT recorded in the s1 LR form and this	13. Alkaline phosphatase	
hepatic panel (visit s2) must be at least 30 days apart, but this hepatic panel may pre-date the ALT recorded on the visit s1 LR form.	a. Upper limit of normal:	
8. Date of blood draw for hepatic panel:	b. Lower limit of normal:	
	U/L	
day mon year		
9. Bilirubin (total):		
10. Bilirubin (conjugated or direct):		

C. Vitamin B₁₂, free fatty acid, leptin, and C-reactive protein

14. Date of blood draw for vitamin B₁₂, free fatty acid, leptin, and C-reactive protein (all on serum):

day	mon	year

Date must be within 3 months of screening.

15. Vitamin B₁₂ (if provided in pmol/L, multiply by 1.35 to convert to pg/ml):

		•	
 	pg/mL	-	-

16. Free fatty acid:

μmol/L	

17. Leptin:

•	
ng/mL	

18. C-reactive protein (if result is reported as normal but below your lab's detectable level, enter the *cutoff for your lab's detectable level):*

•	
ma/dI	
mg/dL	

If units reported are mg/L, divide by 10 to convert to mg/dL.

D. Prothrombin time, GGT and HbA1c

19. Date of blood draw for prothrombin time, GGT, and HbA1c:

day	mon	year
Date must be within 3	months of scr	eening.

- **20.** Prothrombin time (PT):
- **21.** International normalized ratio (INR):

		•	
	•		

22. Gamma glutamyl transferase (GGT):

U/L	
•	
 0/2	

E. Oral glucose tolerance test

The oral glucose tolerance test will be performed in the morning after a 12-hour overnight fast. Baseline blood sample will be obtained for measurements of serum glucose, insulin, and C peptide. Blood samples will be obtained at 2 hours (120 minutes) for the measurement of serum glucose and insulin after oral administration of flavored glucose solution in a dose of 2 g/kg (75 g maximum).

24. Date of blood draw for OGTT:

day	mon	year
. 1	.1 C	

Date must be within 3 months of screening.

25. OGTT results at baseline

a. Serum glucose (if fasting glucose 126 mg/dL or greater, patient is ineligible):

	mg/dL
b. Serum insulin:	<u>Φ</u>
c. Serum C peptide:	<u> </u>

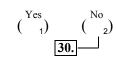
26. OGTT results at 2 hours (if 2-hour glucose ≥ 200 mg/dL, patient is ineligible)

	mg/qL
b. Serum insulin:	•
	μU/mL

F. Pregnancy test

27. Is pregnancy test applicable:

a. Serum glucose:



ng/mL

28. Date of urine collection (or blood draw):

day	mon	year
Date must be the same	e dav as date d	of visit.

29. Pregnancy test results (if pregnancy test is positive at s1 or s2, patient is ineligible):

Positive	(
Negative	(2

23. HbA1c:

G. Eligibility check

30. Was the patient found to be ineligible based on ALT (item 12), fasting serum glucose (item 25a), 2-hour glucose (item 26a), or pregnancy test (item 29):



H. Administrative information

day

31. Study Physician PIN:
32. Study Physician signature:
33. Clinical Coordinator PIN:
34. Clinical Coordinator signature:
35. Date form reviewed:

mon

year

MA - Modifiable Activity Questionnaire

Purpose: To obtain the patient's physical activity.

When: Visits s2, f048, f096, and f120.

Administered by: Interview administered (8-12 yrs) or self-administered (13-17 yrs). Parents may assist with completion, if needed. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient.

Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-3. The patient should meet with the interviewer, be trained in completion of the form, and then should complete pages 2-3. If needed, the Clinical Coordinator may administer the interview to the patient. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B below.

4.	Center, patient, and	l visit ident	ification	B. Administrative information
1.	Center ID:			(To be completed by the Clinical Coordinator after survey is completed).
2.	Patient ID:			8. How was the questionnaire completed: Self-administered by patient/parent (, 1)
3.	Patient code:			10.
4.	Date of visit (date patient completed the form):		leted the form):	Interview in English (2) Interview with translator (3)
	-	month		9. Who was the respondent (check all that apply) a. Patient: b. Patient's mother or female guardian: (1)
5.	Visit code:			c. Patient's father or male guardian: d. Other, <i>specify</i> :
6.	Form & revision:	_	m a 1	
				10. Clinical Coordinator
7.	Study:		TONIC 3	a. PIN:
				b. Signature:
				11. Date form reviewed:
				day month year

Affix Label Here
Patient ID:
Patient code:
Visit code:

Modifiable Activity Questionnaire

(Items 1-11 are reserved for clinic use.)

12.	How many times in the past 14 days have you done at least 20 minutes of exercise <u>hard</u> enough to make you
	breathe heavily and make your heart beat fast? (Hard exercise includes, for example, playing basketball,
	jogging, or fast bicycling; include time in physical education class)?

	Circle one
None	1
1 to 2 days	2
3 to 5 days	
6 to 8 days	
9 or more days	

13. How many times in the past 14 days have you done at least 20 minutes of <u>light</u> exercise that <u>was not</u> enough to make you breathe heavily and make your heart beat fast? (Light exercise includes playing basketball, walking or slow bicycling; include time in physical education class)?

and or ore, energy mercure and in projection education enussy.	Circle one
None	1
1 to 2 days	2
3 to 5 days	3
6 to 8 days	4
9 or more days	5

14. During a normal week how many <u>hours a day</u> do you watch television and videos, or play computer or video games, or use the computer for other activities before or after school?

o games, or use the compater for other activities series of after senious.	
	Circle one
None	1
1 hour or less	2
2 to 3 hours	3
4 to 5 hours	4
6 or more hours	5

15. During the past 12 months, how many team or individual <u>sports</u> or activities did you participate in on a <u>competitive</u> level, such as varsity or junior varsity sports, intramurals, or out-or-school programs?

	Circle one
None	1
1 activity	2
2 activities	3
3 activities	4
4 or more activities	
What activities did you compete in?	

Affix Label Here
Patient ID:
Patient code:
Visit code:

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

16.			ST YEAR. Do not include time spent in school ou participated in during the last year.			
	 01. Aerobics 04. Basketball 07. Cheerleading 10. Garden/Yard Work 13. Ice Skating 16. Skateboarding 19. Softball 22. Tennis 25. Weight Training (Competitive) 	 () 02. Band/Drill Team () 05. Bicycling () 08. Dance Class () 11. Gymnastics () 14. Roller Skating () 17. Snow Skiing () 20. Street Hockey () 23. Volleyball () 26. Wrestling 	 () 03. Baseball () 06. Bowling () 09. Football () 12. Hiking () 15. Running and Exercise () 18. Soccer () 21. Swimming () 24. Water Skiing () 27. Others: 			
	List each activity that you checked above in the "Activity" box below. Check the months you did each activity and then estimate the amount of time spent in each activity.					

F E J U S E P O C T D E A P J U A U N O M Months Days Minutes M Activity Activity A Α per per per Code # Day В R N L G Year Week

17.	Today's date:	

MR - MRI Report

Purpose: To record liver imaging study results.

When: Visits s2 and f096, if needed. Administered by: Clinical Coordinator.

Instructions: Upper abdominal MRI is optional. Complete for an upper abdominal MRI done in the year prior to starting screening for TONIC or during screening for TONIC (s2 visit) or done during the f096 window (f096 visit). Answer the items based on review of the imaging report; the Study Physician must review and approve the findings recorded on this form. Attach a copy of the original MR report to this form.

A. Center, patient, and visit identification	k. Other features of portal	/
1. Center ID:	(specify): -	(1)
2. Patient ID:	-	
3. Patient code:	l. Other abnormality (speci	(₁):
4. Date of visit:		
day mon year	m. None of the above:	(1)
,	C. Administrative information	1
5. Visit code:	- 10. Study Physician PIN:	
6. Form & revision:mr	_	
	11. Study Physician signature:	
7. Study: TONIC		
B. Upper abdominal MRI	12. Clinical Coordinator PIN:	
8. Date of upper abdominal MRI:	13. Clinical Coordinator signat	ure:
day mon year		
9. Findings suggestive of NAFLD,	14. Date form reviewed:	
cryptogenic cirrhosis, or others of		
significance (check all that apply)		mon year
a. Fatty infiltration:)	
b. Cirrhosis:)	
c. Hepatomegaly:)	
d. Hepatic mass: ()	
e. Hepatic hemangioma: ()	
f. Hepatic cyst: ()	
g. Intrahepatic biliary dilatation: ()	
h. Extrahepatic biliary dilatation: (
i. Splenomegaly:)	
i. Ascites:)	

MV - Missed or Incomplete Visit

Purpose: Record reason(s) for missed or incomplete visit.

When: At the close of a visit window for any missed followup visit or for any followup visit with specific forms not completed. Use visit code f004, f012, f024, f036, f048, f060, f072, f084, f096 and f120.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in

missing forms) within the time window for the visit.

Δ	Center	natient	and visit	identif	ication
A.	Center,	Dauent.	anu visit	паенин	icauon

- **1.** Center ID: ____ ____
- **2.** Patient ID: ____ __ ___
- **3.** Patient code: ____ ___
- 4. Date of visit:

	=	_
day	mon	year

- **5.** Visit code: __f_ ___ ___
- 7. Study: TONIC <u>3</u>

B. Reason for completion of this form

8. Was the entire visit missed:

$$\binom{\text{Yes}}{1} \qquad \binom{\text{No}}{2}$$

C. Missed visit information

- 9. Reason for missed visit (check all that apply)
 - **a.** Patient was ill:
 - **b.** Patient was temporarily away from area:
 - **c.** Patient refused to return: (1)
 - **d.** Patient has permanently moved from the area:
 - e. Unable to contact patient:
 - **f.** Other (specify):

specif	
speci	

- **10.** Steps taken to avoid missing the visit *(check all that apply)*
 - **a.** Telephoned patient: (1)
 - **b.** Mailed reminder card:
 - **c.** Other (specify):

specif	y



D. Missed form information

11. Check form(s) not completed (check required forms that were missed)		
a. Food Questionnaire Documentation (BD):	(1)
b. Blood Processing for Plasma and Serum (BP):	(1)
c. DEXA Scan Report (DX):	(1)
d. Followup Medical History (HI):	(1)
e. Symptoms of Liver Disease (Children) (LP):	(1)
f. Laboratory Results - Tests Done During Screening and Followup (LR):	(1)
g. Modifiable Activity Questionnaire (MA):	(1)
h. MRI Report (MR):	(1)
i. Physical Examination (PE):	(1)
j. Focused Physical Examination (PF):	(1)
k. Pediatric Quality of Life: Parent of adolescent age 13-17 (PQ):	(1)
1. Pediatric Quality of Life: Parent of child age 8-12 (PR):	(1)
m. Pediatric Quality of Life: Child age 8-12 (PW):	(1)
n. Pediatric Quality of Life: Adolescent age 13-17 (PY):	(1)
o. Study Drug Dispensing and Return (RD):	(1)
p. Liver Biopsy Materials Documentation (SD):	(1)
q. Other (specify):	(1)
specify		
12. Reason form(s) not completed (check all that apply)		
a. Patient was ill:	(1)
b. Patient refused procedure:	(1)
c. Parent refused procedure:	(1)
d. Procedure forgotten:	(1)
e. Other (specify):	(1)
specify		

13.	Attempts made to complete form(s) (check all that apply)		
	a. Attempted to reschedule procedure:	(1)
	b. Attempted to collect interview data by phone from patient/family:	(1)
	c. Attempted to gain patient/parent cooperation:	(1)
	d. Other (specify):	(1)
	specify		
E. A	dministrative information		
14.	Clinical Coordinator PIN:		
15.	Clinical Coordinator signature:		
16.	Date form reviewed:		
	day mon	year	

PE - Physical Examination

Purpose: Record detailed physical exam findings.

When: Visits s1, f048, f096, and f120.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurements are found in TONIC SOP, Part I. In brief: Height, weight, waist and hips all should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other. Triceps skin fold and mid-upper arm circumference measurements should be done on the right arm.

One of the eligibility criteria for TONIC is the ability to swallow TONIC study medications. If you are unsure about the patient's ability to swallow the study medication, you may ask the patient to swallow a capsule from the bottle of placebo metformin sent to the clinical center by the DCC before the start of TONIC. The physical examination might be a logical time to ask the patient about this/ask for a demonstration. If the patient is unable to swallow the placebo and is ineligible (item 44=2), the PE form should not be keyed.

A. Center, patient, and visi	t identification	9. Weight (shoes off)	
1. Center ID:		a. Weight, 1st measurement:	
2. Patient ID:		b. Weight, 2nd measurement:	_ •
3. Patient code:		c. Units:	
4. Visit date:		Pounds Kilograms	$\begin{pmatrix} & & & \\ & & 1 \end{pmatrix}$
day	mon year	10. Waist (standing, at midpoint betwee	n highest point
5. Visit code:		of iliac crest and lowest part of c repeat waist measurements until measurements within 4 in (10.2 cm)	you have two
6. Form & revision:	_pe1_	a. Circumference, 1st measurement	t:
7. Study:	TONIC_3_	b. Circumference, 2nd measuremen	
B. Measurements		waist circu	 ımference
8. Height (shoes off)		c. Units: Inches	()
a. 1st measurement:	•	Centimeters	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$
b. 2nd measurement:	•		
c. Units:			
Inches Centimeters	$\begin{pmatrix} & & & \\ & & & \\ & & & \end{pmatrix}$		

11. Hip (standing, at fullest part of the hips; repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other)		16.	Respiratory rate:	breaths/mir	nute	
	a. Circumference, 1st measurement:		C. 1	Examination findings		
	hip circum	eference	17.	Skin:		
	b. Circumference, 2nd measuremen			Normal	()
	b. Circumerence, 2nd measuremen	•		Normal	20	-1 <i>)</i>
	hip circum	ference		Abnormal	20.	2)
	c. Units:			Tonomia	(2)
	Inches	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	18.	Acanthosis nigricans (check only on	ie):	
	Centimeters	$\begin{pmatrix} & & & & & & & & & & & & & & & & & & &$		Absent (not detectable on close insp	pection) (0
12.	Triceps (right arm, with elbow externelaxed; repeat skin fold measurem have two within 10 mm of each mid-upper arm circumference until	ents until you other; repeat		Present (clearly present on close inspection, not visible to casual obsextent not measurable)	erver,	1)
	within 1.5 in (3.8 cm) of each other) a. Skin fold, 1st measurement:			Mild (limited to base of skull, not extending to lateral margins of nect < 3 inches in breadth)	k, (2)
	b. Skin fold, 2nd measurement:	1		Moderate (extending to lateral margof neck, 3-6 inches in breadth, not v from patient's front)	gins visible	3)
	c. Mid-upper arm circumference, 1s			Severe (extending anteriorly, > 6 in breadth, visible from front)	iches in (4)
	measurement:	•	19.	Other skin abnormality (check all th	iat apply)	
	arm cir	cumference		a. Jaundice:	(1)
	d. Mid-upper arm circumference, 2n	nd			(
	measurement:	•		b. Palmar erythema:	(1)
	arm cir	cumference		c. Spider angiomata:	(1)
	e. Units for arm circumference:			d. Other (specify):	(1)
	Inches	(1)				
	Centimeters	(2)		e. None of the above:	(
13.	Temperature (Oral)					
	-	_	20.	Head, eyes, ears, nose, throat:		
	a. Degrees:	- 		Normal	(1)
	b. Scale:				22.	J
	Fahrenheit	()		Abnormal	(2)
	Centigrade	$\begin{pmatrix} & & 1 \\ & & 1 \end{pmatrix}$	21	Abnormality of the head, eyes, nose		
	Centigrade	(2)	21.	throat	,	
14.	Blood pressure			(check all that apply)		
				a. Jaundice:	(1)
	a. Systolie:			b. Other (specify):	(.)
		mmHg		("F (-02))"	(17
	b. Diastolic:	mmHg		specify		—
15	Dagting radial mulas					
15.	Resting radial pulse:	beats/minute				

22. Neck:

Normal	(
Abnormal	23.

specify abnormality

23. Lymphatic:

Normal		()
Abnormal		24. (₂)
	specify abnormality	

24. Chest and lungs:



25. Heart:

Normal		(1
Abnormal		26. (₂)
	enecify abnormality	

26. Abdomen:

Normal	(1)
Abnormal	28. (₂)

27.

Abdomen abnormality (check all that apply)		
a. Ascites:	(1)
b. Obese:	(1)
c. Other (specify):	(1)
specify		

28. Liver and spleen:

Normal	(1)
Abnormal	30. (₂)

29. Abnormality of liver or spleen (check all that ap-

a. Hepatomegaly: (if checked, span from right midclavicular line):	(1)
une).		

	cm		
b. Splenomegaly:		(1
e. Other (specify):		(1

	\ 1	007		•	17
			specify		

30. Extremities:

1)

2)

Not performed	()
Normal	32. (₁)
Abnormal	32. (₂)

31. Abnormality of the extremities *(check all that apply)*

a. Contractures:	(1
b. Muscle wasting:	(1
c. Palmar erythema:	(1
d. Pedal edema:	(1



32. Genitourinary/pelvis:

Not performed	()
Normal	33.
Abnormal	33. (2)
SDG	ecify

33. Nervous system:

Not performed	(0
Normal	35. (1)
Abnormal	[35.] (₂)

34. Abnormality of the nervous system			Female Tanner Staging
(check all that apply): a. Mental status abnormal:	(1)	40. Breast stage: 1-5
b. Asterixis:	(1)	1-5
c. Other (specify):	(1)	41. Pubic hair stage:
specify D. Tanner Staging			42. Has menarche occurred: (Yes (1) (No (2) 44.
35. Is Tanner staging required for this participant (Note: Required at screening visit.) (check only one):	3		43. What was the participant's age at menarche: age in years
36. Is the patient female: Yes (1)	44.	12	 E. Ability to swallow study medication (At the randomization visit the Study Physician/Clinical Coordinator will be asked to provide assurance that the patient is able to swallow the TONIC study medication; if needed, you could ask the patient to swallow a capsule from the placebout metformin provided by the DCC). 44. Was the patient able to swallow a placebo metformin capsule (check only one): Yes, patient was able to swallow capsule No, patient was unable to swallow the
Male Tanner Staging 37. Genital stage:	_		Did not ask for a demonstration at this time
C	1	1-5	F. Administrative information
38. Testicular volume (smallest of right and left):	cc		45. Study Physician PIN:
39. Pubic hair stage:		1-5	46. Study Physician signature:
[.	44.		47. Clinical Coordinator PIN:
			48. Clinical Coordinator signature:
			49. Date form reviewed:

year

day

mon

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.

When: Visits f004, f012, f024, f036, f060, f072, and f084. Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurement are found in the TONIC SOP Part I. In brief: height, weight, waist and hips should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

A. Center, patient, and visi	it identific	cation	10. Waist (standing, at midpoint be	etween highest point
1. Center ID:			of iliac crest and lowest par repeat waist measurements i measurements within 4 in (10	ıntil you have two
2. Patient ID:			a. 1st measurement:	_
3. Patient code:	_		b. 2nd measurement:	
4. Visit date:			c. Units:	
<u>_</u>		_	Inches	()
day	mon	year	Centimeters	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$
5. Visit code:		 pf1_	11. Hip (standing, at fullest part of measurements until you have within 4 in (10.2 cm) of each of	two measurements
6. Form & revision:	=	<u>p </u>	, , ,	nner)
7. Study:		TONIC 3	a. 1st measurement:	•
B. Measurements			b. 2nd measurement:	•
8. Height (shoes off)			c. Units:	
a. 1st measurement:			Inches	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
		•	Centimeters	(2)
b. 2nd measurement:		•	12. Temperature (oral)	
c. Units:			a. Degrees:	<u> </u>
Inches		$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
Centimeters		$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	b. Scale:	
O W 1 1 / 1 00			Fahrenheit:	(1)
9. Weight (shoes off)			Centigrade:	(₂)
a. 1st measurement:		•	13. Blood pressure	
b. 2nd measurement:			a. Systolic:	
c. Units:			b. Diastolic:	
Pounds		()	b. Diagonio.	mmHg
Kilograms		()		

14. Resting radial pulse:	beats/minute		D. Administrative information	
15. Respiratory rate:	breaths/minu	 ute	18. Study Physician ID:19. Study Physician signature:	
C. Liver signs			, , ,	
16. Liver and spleen:				
Normal	(1)	20. Clinical Coordinator ID:	
Abnormal	18.	2)	21. Clinical Coordinator signature:	
17. Abnormality (check all that app	ply)			
a. Ascites:	(1)		
b. Asterixis:	(1)	22. Date form reviewed:	
c. Contractures:	(1)		1/00
d. Hepatomegaly:	(1)	uay iiioii	yea
If Yes, span from right midcl	lavicular line:			
	· •	_		
e. Jaundice:	cm (1)		
f. Muscle wasting:		1)		
g. Palmar erythema:	,	1)		
h. Pedal edema:		1)		
i. Spider angiomata:	,	1)		
j. Splenomegaly:	(1)		
k. Other, (specify):	(1)		

specify abnormality

PQ – Pediatric Quality of Life: Parent Report for Teens (Age 13-17)

Purpose: To obtain the patient's quality of life.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of teens, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #8, Instructions for Pediatric Quality of Life (Forms PQ, PR, PS, and PT) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be re-attached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

. Ce	Center, patient, and visit identification				B. Administrative information (To be completed by Clinical Coordinator after				
1.	Center ID:			,	o be completed by Clinical Coordinator after urvey is completed.)				
2.	Patient ID:			8.	How was the Pediatric Quality of Life questionnaire completed:				
3.	Patient code:				Self-administered in English	(,		
4.	Date form completed:		_		Self-administered in Spanish Interview in English Interview in Spanish	((2)		
	day	mon	year		interview in Spainish	(4)		
5.	Visit code:			9.	Clinical Coordinator a. PIN: b. Signature:				
6.	Form & revision:	<u> </u>	<u>q</u> 1		8				
7.	Study:		TONIC 3	10.	Date form reviewed:				
					day mon ye	ar			

	Affix label here		
Q - Pediatric Quality of Life: ent Report for Teens (Age 13-17)	Patient ID: Patient code: Visit code:		

P Pare

In the past **ONE month**, how much of a **problem** has your teen had with...

PHYSICAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in sports activity or exercise:	0	1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores around the house:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:	0	1	2	3	4

ЕМО	TIONAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

soc	IAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	Getting along with other teens:	0	1	2	3	4
25.	Other teens not wanting to be his or her friend:	0	1	2	3	4
26.	Getting teased by other teens:	0	1	2	3	4
27.	Not able to do things that other teens his or her age can do:	0	1	2	3	4
28.	Keeping up with other teens:	0	1	2	3	4

PedsQl 4.0 - Parent (13-17)

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Affix label here
Patient ID:
Patient code:
Visit code:

SCH	OOL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	Keeping up with schoolwork:	0	1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PR – Pediatric Quality of Life: Parent Report for Children (Age 8-12)

Purpose: To obtain the patient's quality of life.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of child, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #8, Instructions for Pediatric Quality of Life (Forms PQ, PR, PS, and PT) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be re-attached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	enter, patient, and visit iden	tification		Iministrative information To be completed by Clinical Coordinato	r after
1.	Center ID:		,	urvey is completed.)	
2.	Patient ID:		8.	How was the Pediatric Quality of Life questionnaire completed:	:
3.	Patient code:				()
4.	Date form completed:			Self-administered in English Self-administered in Spanish Interview in English Interview in Spanish	$\begin{pmatrix} & & & 1 \\ & & & 2 \\ & & & & 3 \\ & & & & 4 \end{pmatrix}$
	day mon	year		merview in Spainsii	(4)
5.	Visit code:		9.	Clinical Coordinator a. PIN: b. Signature:	
6.	Form & revision:	<u>p</u> <u>r</u> <u>1</u>			
7.	Study:	TONIC 3	10.	Date form reviewed:	
				aay	year

Affix le	abel here
Patient ID:	
Patient code:	
Visit code:	

PR - Pediatric Quality of Life: Parent Report for Children (Age 8-12)

In the past **ONE month**, how much of a **problem** has your child had with...

PHYSICAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in sports activity or exercise:	0	1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores around the house:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:	0	1	2	3	4

ЕМО	TIONAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

Soc	IAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	Getting along with other children:	0	1	2	3	4
25.	Other kids not wanting to be his or her friend:	0	1	2	3	4
26.	Getting teased by other children:	0	1	2	3	4
27.	Not able to do things that other children his or her age can do:	0	1	2	3	4
28.	Keeping up when playing with other children:	0	1	2	3	4

PedsQI 4.0 - Parent (8-12)

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Affix label here
Patient ID:
Patient code:
Visit code:

SCH	OOL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	Keeping up with schoolwork:	0	1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PW – Pediatric Quality of Life: Child Report (Age 8-12)

Purpose: To obtain the patient's quality of life.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #7, Instructions for Pediatric Quality of Life (Forms PW and PY) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	nter, patient, and visi	t identificat	ion		lministrative info To be completed by	ormation y Clinical Coordina	ıtor after	
1.	Center ID:			Si	ırvey is completed	!.)		
2.	Patient ID:			8.	How was the Pe questionnaire co	diatric Quality of Li ompleted:	ife	
3.	Patient code:				G-16 - 1	Alta Paultal	(`
4.	Date form completed:		_		Self-administere Self-administere Interview in Eng Interview in Spa	ed in Spanish glish	(1) 2) 3) 4)
	day	mon	year		interview in Spe		,	4)
5.	Visit code:			9.	Clinical Coordinga. PIN:b. Signature:			
6.	Form & revision:	<u> </u>	w1		2.8			
7.	Study:		TONIC 3	10.	Date form review	wed:		
						mon	year	

Affix le	abel here
Patient ID:	
Patient code:	
Visit code:	

PW - Pediatric Quality of Life: Child Report (Age 8-12)

In the past **ONE month**, how much of a **problem** has this been for you...

ABOUT MY HEALTH AND ACTIVITIES (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. It is hard for me to walk more than one block:	0	1	2	3	4
12. It is hard for me to run:	0	1	2	3	4
13. It is hard for me to do sports activity or exercise:	0	1	2	3	4
14. It is hard for me to lift something heavy:	0	1	2	3	4
15. It is hard for me to take a bath or shower by myself:	0	1	2	3	4
16. It is hard for me to do chores around the house:	0	1	2	3	4
17. I hurt or ache:	0	1	2	3	4
18. I have low energy:	0	1	2	3	4

ABOUT MY FEELINGS (problems with)	Never	Almost Never	Some- times	Often	Almost Always
19. I feel afraid or scared:	0	1	2	3	4
20. I feel sad or blue:	0	1	2	3	4
21. I feel angry:	0	1	2	3	4
22. I have trouble sleeping:	0	1	2	3	4
23. I worry about what will happen to me:	0	1	2	3	4

How	I GET ALONG WITH OTHERS (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	I have trouble getting along with other kids:	0	1	2	3	4
25.	Other kids do not want to be my friend:	0	1	2	3	4
26.	Other kids tease me:	0	1	2	3	4
27.	I cannot do things that other kids my age can do:	0	1	2	3	4
28.	It is hard to keep up when I play with other kids:	0	1	2	3	4

PedsQI 4.0 - (8-12)

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Patient ID:
Patient code:
Visit code:

ABOUT SCHOOL (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29. It is hard to pay attention in class:	0	1	2	3	4
30. I forget things:	0	1	2	3	4
31. I have trouble keeping up with my schoolwork:	0	1	2	3	4
32. I miss school because of not feeling well:	0	1	2	3	4
33. I miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

A

PY – Pediatric Quality of Life: Teen Report (Age 13-17)

Purpose: To obtain the patient's quality of life.

When: Visits s2, f048, f096, and f120.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #7, Instructions for Pediatric Quality of Life (Forms PY and PW) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

. Ce	enter, patient, and visit id	lentification	n		I ministrative information To be completed by Clinical Coordinator o	aftar	
1.	Center ID:				arvey is completed.)	ijiei	
2.	Patient ID:			8.	How was the Pediatric Quality of Life questionnaire completed:		
3.	Patient code:				Self-administered in English	(1)
4.	Date form completed:				Self-administered in Spanish Interview in English Interview in Spanish	(2) 3)
	day m	non	year		interview in Spanish	(4)
5.	Visit code:			9.	Clinical Coordinator a. PIN: b. Signature:		
6.	Form & revision:	<u> </u>	<u>y</u> <u>1</u>		b. Oighaidic.		
7.	Study:		TONIC 3	10.	Date form reviewed:		
					day mon	year	

PY	- Pediatric Quality of Life:
	Adolescent (Age 13-17)

Affix i	label here
Patient ID:	
Patient code:	
Visit code:	

In the past **ONE month**, how much of a **problem** has this been for you...

ABOUT M	IY HEALTH AND ACTIVITIES (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. It is	hard for me to walk more than one block:	0	1	2	3	4
12. It is	hard for me to run:	0	1	2	3	4
13. It is	hard for me to do sports activity or exercise:	0	1	2	3	4
14. It is	hard for me to lift something heavy:	0	1	2	3	4
15. It is	hard for me to take a bath or shower by myself:	0	1	2	3	4
16. It is	hard for me to do chores around the house:	0	1	2	3	4
17 . I hui	rt or ache:	0	1	2	3	4
18 . I hav	ve low energy:	0	1	2	3	4

ABOUT MY FEELINGS (problems with)	Never	Almost Never	Some- times	Often	Almost Always
19. I feel afraid or scared:	0	1	2	3	4
20. I feel sad or blue:	0	1	2	3	4
21. I feel angry:	0	1	2	3	4
22. I have trouble sleeping:	0	1	2	3	4
23. I worry about what will happen to me:	0	1	2	3	4

How	I GET ALONG WITH OTHERS (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	I have trouble getting along with other teens:	0	1	2	3	4
25.	Other teens do not want to be my friend:	0	1	2	3	4
26.	Other teens tease me:	0	1	2	3	4
27.	I cannot do things that other teens my age can do:	0	1	2	3	4
28.	It is hard to keep up with my peers:	0	1	2	3	4

PedsQl 4.0 - (13-17)

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Affix label here					
Patient ID:					
Patient code:					
Visit code:					

ABOUT SCHOOL (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29. It is hard to pay attention in class:	0	1	2	3	4
30. I forget things:	0	1	2	3	4
31. I have trouble keeping up with my schoolwork:	0	1	2	3	4
32. I miss school because of not feeling well:	0	1	2	3	4
33. I miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

RC - Rescreen in TONIC

Purpose: To rescreen a patient who was previously found to be ineligible for TONIC due to a temporary ineligibility. This form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 112-day screening window is reckoned from). The original RG form completed for the patient must remain in the data system. New screening phase tube and questionnaire labels will be available for printing upon keying this form.

When: Visit code s1.

Administered by: Clinical Coordinator.

Respondent: None.

Instructions: Complete this form for a patient who was previously found to be ineligible for TONIC due to a temporary ineligibility and who now wants to rescreen for TONIC. In general, the patient must complete all TONIC screening data collection anew and all previously keyed TONIC screening forms should be deleted from the data system except the RG and possibly the BC and CG forms. Update sections B, C, D, and G of the RG form and update the keyed record (you cannot delete the RG form). If blood was collected successfully for the Genetics Repository, a new sample does not need to be collected and the previously completed BC and CG forms may remain unchanged in the data system. Plasma and serum must be collected anew. If the same liver biopsy is being used to satisfy eligibility now and slides were sent to the DCC, additional slides do not need to be sent. The pathologist should rescore the biopsy and new SD and HF forms should be completed transcribing the slide numbers as needed.

A. Center, pat	ient, and vi	sit identifica	tion	C. Administ	rative infor	mation	
1. Center ID:				9. Clinical	Coordinator	PIN:	
2. Patient ID:				10. Clinical	Coordinator	signature:	
3. Patient cod	le:						
4. Date of vis	sit:			11. Date for	m reviewed:		
	day	mon	year		day	mon	year
5. Visit code:		_s1					
6. Form & re	vision:	<u>r</u>	<u>c</u> 1				
7. Study:		,	TONIC 3				
B. TONIC par	ticipation						
8. Date in iter form:	m 4 of origi	nal TONIC R	G				
	day	mon	year				

RD - Study Drug Dispensing and Return

Keyed: ()

Purpose: To record dispensing and return of study drugs.

When: Visits rz, f004, f012, f024, f036, f048, f060, f072, f084, and f096. Use visit code "n" if drugs are dispensed or returned at a time other than a regular study visit or if a second form is needed at a visit to document returned study drugs.

Administered by: Pharmacist or Clinical Coordinator, reviewed by Study Physician.

Instructions: This form documents dispensing of study drug, return of unused study drug, and return of empty study drug bottles. This form is required at visit rz and every scheduled followup visit thereafter except visit f120. It may be used at unscheduled visits as needed (use visit code n).

Study drugs are dispensed in the quantities specified below:

Visit	No. of TM series bottles	No. of TE series bottles	Comment
rz	2	2	12 week supply
f012	2	2	12 week supply
f024	2	2	12 week supply
f036	2	2	12 week supply
f048	2	2	12 week supply
f060	2	2	12 week supply
f072	2	2	12 week supply
f084	2	2	12 week supply

The patient should be queried about return of empty study drug bottles at all study visits; return of unused study drug is required at the visits at which study drug is dispensed. Each time a patient returns a used study drug bottle to the clinical center, the pharmacist or the clinical coordinator should count and record the remaining number of capsules or softgels in study drug bottles. This form allows recording of the return of up to eight bottles (four TM series and four TE series). If more than four bottles of either series are returned at a time, complete a second form (using visit code "n") to record the information for the remaining bottles.

A. Center, patient, and visit identification

- 1. Center ID: _____ ____
- **3.** Patient code:
- 4. Date of visit:

day mon year

- **5.** Visit code:
- **6.** Form & revision: <u>r</u> <u>d</u> <u>1</u>
- 7. Study:

B. Study drug dispensing

8. Is this a second form for returning additional drug bottles at this visit:

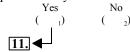
Yes

No

(1)



9. Will study drug be dispensed today:



- **10.** Reason for not dispensing study drug *(check all that apply)*
 - a. Not a scheduled study drug dispensing visit: (1)
 - **b.** Study physician-directed treatment interruption/termination: (1)
 - **c.** Unwillingness of the participant to take study drugs:
 - **d.** Other (specify): (1)

specify	
	<u>16.</u> ◀

TONIC 3

TM series

Bottle tear-off label

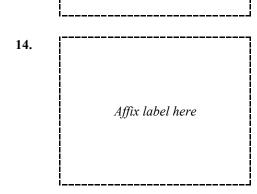
11.

Affix label here

12.

Affix label here

TE series 13. Affix label here

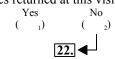


15. How were the study drugs dispensed to the patient *(check only one)*:

In person Mail Other (specify)		((1, 2, 3,
	specify		

C. Study drug return

16. Were any TM series bottles returned at this visit:



17. Number of TM series bottles returned (if more than 4 bottles returned, complete a second RD form):

(1-4)

	a. Bottle No.	b. Number of capsules returned
18.	TM	(00-100)
19.	TM	(00-100)
20.	TM	
21.	TM	(00-100)

	Patient ID:

22. Were any TE series bottles returned at this visit:



23. Number of TE series bottles returned (*if more than 4 bottles returned, complete a second RD form*):



	a. Bottle No.	b. Number of softgels returned
24.	TE	(00-100)
25.	TE	(00-100)
26.	TE	(00-100)
27.	TE	

D. Remaining bottles

28. Are any additional bottles being returned:



(00-100)

*If yes, complete a second RD form using visit code "n."

E. Administrative information

- **29.** Clinical Coordinator PIN: _____ ___
- **30.** Clinical Coordinator signature:

31. Date form reviewed:

_		_
day	mon	vear

RG - Registration

Purpose: To register patient as candidate for enrollment in TONIC and to assign a patient ID number. This is the first form completed for a TONIC patient. The Registration Form must be the first form keyed, before any other TONIC forms.

When: At first screening visit (s1). Administered by: Clinical Coordinator. Respondent: Patient and guardian.

Instructions: Use Flash Cards as instructed. Do not assign a new ID if patient has previously been assigned an ID for a NASH CRN study. If is checked for any item, the patient is not eligible for TONIC and the form should not be keyed.

A. Center,	patient and	d visit	identific	ation
1 Center	· ID·			

- 1. Center ID: ____ ____
- **2.** Patient ID: ____ ____
- **3.** Patient code: ____ ___
- **4.** Visit date:
- 5. Visit code: _s_ _1 ___ ___

mon

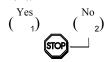
- **6.** Form & revision: __r__g__1__
- 7. Study: TONIC <u>3</u>

B. Consent

8. After reviewing the existing records (e.g., liver biopsy, elevated aminotransferases, and/or history) does the study physician feel that the patient may be suitable for the study:



9. Has the patient's guardian signed the TONIC informed consent statement:



10. Has the patient signed the TONIC informed assent statement:

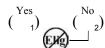
Yes	(.
No	(;
	STOP —
Not using assent	(;
Not using assent for this age child	(,

C. Information about patient

11. Date of birth:

_		
day	month	year
Record	4-digit vear for da	te of birth.

- **13.** Is the patient's age at least 8 years old and less than 18 years:



14. Gender:

Male	(1/
Female	(2)

15. Ethnic category (show the patient/guardian Flash Card #1 and ask the respondent to pick the category that describes the patient best; check only one):

Hispanic or Latino or Latina

Not Hispanic, not Latino, not Latina

17.

16.	What describes the patient's Hispanic,			20. Current age of patient's female guardian		
	Latino, or Latina origin best (show the pa- tient/guardian Flash Card #1 and ask the respon-		stepmother, or other) (show patient/g Flash Card #4; check only one):	<i>şuard</i>	ian	
	dent to pick the subcategory that best desc patient's Hispanic, Latino, or Latina orig only one):			Not applicable (mother is deceased or patient has no stepmother or female	(`
	Mexican	(1)	guardian)	(0)
	Puerto Rican	$\tilde{}$	2)	19 or younger	(1)
	Cuban	(20-29 years	(2)
		(3)	30-39 years	(3)
	South or Central American	(4)	40-49 years	(4)
	Other Spanish culture or origin	(₅)	50-59 years	Ì	5)
	specify			60 years or older	(6)
	specify			21 Highest advectional level achieved by		
17.	Racial category (show the patient/guardicard #2 and ask the respondent to pick gory or categories that describe the paticheck all that apply)	the co	ate-	21. Highest educational level achieved by patient's female guardian (mother, stepn other) (show patient/guardian Flash Coeducation of female guardian is unknown as "n"; check only one):	ard #5	5; if
	a. American Indian or Alaska Native:	(1)	Never attended school	(0
	b. Asian:	(1)	Did not complete high school	(1)
	c. Black, African American, Negro, or			Completed high school	(2)
	Haitian:	(1)	Some college or post high school		
	d. Native Hawaiian or other Pacific			education or training	(3)
	Islander:	(1)	Bachelor's degree or higher	(4)
	e. White:	(1)	22. Current age of patient's male guardian	fath	er,
	f. Patient refused:	(1)	stepfather, or other) (show patient/g Flash Card #4; check only one):		
18.	In what country was the patient born (ch one):	eck d	only	Not applicable (father is deceased or patient has no stepfather or male	(`
	Continental US (includes Alaska) or			guardian)	(0)
	Hawaii	(1)	19 or younger	(1)
	Other, (specify):	(2)	20-29 years	(2)
				30-39 years	(3)
	specify			40-49 years	(4)
				50-59 years	(₅)
19.	Patient's current grade level in school (or			60 years or older	(6)
	home school) (show the patient/guardic Card #3 and ask the respondent to pick gory that describes the patient best; if time, report grade entering in the fall; chone): Grades 1 to 5	the co	ate- mer	23. Highest educational level achieved by patient's male guardian (father, stepfa other) (show patient/guardian Flash Coeducation of male guardian is unknown, "n"; check only one):	ard #5	5; if
	Grades 6-8	Ì	2)	Never attended school	(0
	Grades 9-12	\widetilde{C}	2)	Did not complete high school	(1)
		,	3/	Completed high school	(2)
				Some college or post high school	`	-/
				education or training	(3)
				Bachelor's degree or higher	(4)

Patient ID:	 	

24. Combined annual income before taxes of all members of patient's household (show guardian Flash Card #6 and ask respondent to pick the category that describes the patient's combined household income best; check only one):

Less than \$15,000	(1
\$15,000 - \$29,999	(2
\$30,000 - \$49,999	(3
\$50,000 or more	(4

D. Source of patient

(Clinic staff should pick the best description of the source of patient)

25. Source of patient (check only one):

Bariatric surgery clinic	(01)
Current patient of NASH CRN	
investigator	(02)
Diabetes clinic	(03)
GI/liver clinic	(04)
HMO-based	(05)
Lipid disorders clinic	(06)
Obesity clinic	(07)
Pediatric clinic	(08)
Pediatric weight disorders clinic	(09)
Primary care clinic	(10
Self referral	(11)
Other, (specify):	(12

specify

E. Previous registration in a NASH CRN study

26. Has the patient ever been assigned an ID number in a NASH CRN study:

27. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

a. NAFLD Database:	(1.
b. Other, (specify):	(1.
specify		

28. ID Number previously assigned to patient (record patient ID in item 2):

29. Code previously assigned to patient *(record patient code in item 3):*

31.

F. ID assignment

(If a STOP or ineligible condition was checked in section B, the patient is ineligible and a Patient ID should not be assigned. If the patient was previously registered in a NASH CRN study, a new ID number should not be assigned.)

30. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####,zzz

- G. Administrative information
- **31.** Clinical Coordinator PIN: ____ ___
- **32.** Clinical Coordinator signature:
- **33.** Date form reviewed:

day	mon	year

SD - Liver Biopsy Materials Documentation

Purpose: To document that the liver biopsy required for screening was obtained under the time and medication restrictions required by the protocol. The number and type of slides available for archival at the Data Coordinating Center is noted for both screening and followup biopsies. If slides cannot be archived at the Data Coordinating Center, the source of the slides and the time by which the slides must be returned to the clinical center are recorded.

When: Visits s1, f096, and as needed for biopsies at interim times. During followup, specify the code for the followup visit that is currently open (check the patient's visit time window guide). If no window is open (e.g., right after enrollment), use visit code "n".

By whom: Clinical Coordinator in consultation with the Study Pathologist.

Instructions: This form provides information about the tissue and slides from the biopsy and alerts the DCC to expect receipt of slides from the biopsy at the Data Coordinating Center. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and code, and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60, the borrowed slides should be labeled with removable overlabels with sequence numbers 81-90.

Δ	Center	natient	and vi	ahi tiz	ntifics	ition
Α.	Center.	рацені	and vi	sii iae	HUHCZ	tuon

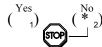
1. Center ID:

- **3.** Patient code: ____ _
- 4. Date form initiated:

 day mon year
- **5.** Visit code ____ __ ___
- **6.** Form & revision: __s__d__2__
- **7.** Study: TONIC <u>3</u>

B. Surgical pathology report

8. Is a copy of the report annotated with the patient's NASH CRN ID number and code and with name blacked out attached to this form:



* Obtain a copy of the report, annotate it, and attach it. You can use one of the pathology labels to annotate the report.

- 9. Biopsy information
 - **a.** Date of biopsy specified on the surgical pathology report:

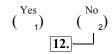
day	mon	year
Lobe specimen obt	ained from	

(check only one):
Right

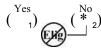
Right	(1.
Left	(2
Unknown	(2

C. Requirements for screening biopsy

10. Is this visit s1:



11. Is the date in item 9 within 6 months (183 days) of the anticipated date of randomization:



* Biopsy date must be within 6 months of randomization.

D. Biopsy specimens and stained slides at the clinical center

12. What stained slides from the biopsy are available at the clinical center (check all that apply)

a. H & E stain:	(
a. II & L Stain.		1

E. Unstained slides to be sent to the DCC

13. Are unstained slides available for sending to the DCC:

$$\begin{pmatrix}
\text{Yes} \\
\text{1}
\end{pmatrix} \qquad \begin{pmatrix}
\text{No} \\
\text{2}
\end{pmatrix}$$

01-60

- 14. How many unstained slides will be sent to the DCC:
- 15. What are the slide sequence numbers for those slides (from the NASH CRN labels on each slide - use permanent labels, sequence numbers 01-60)

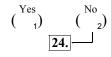
a.	Slide sequence number:	
	•	01-60

b. Slide sequence number:	
	01-60

F. Stained slides to be sent to the DCC

(The institution's stained slides must be sent to the DCC only if fewer than 2 unstained slides will be sent to the DCC)

16. Are any stained slides to be sent to the DCC:

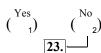


- 17. How many stained slides to be sent to the DCC:
- **18.** Sequence number of slides to be sent to DCC
 - **a.** Slide sequence number of H & E stain:

- **b.** Slide sequence number of Masson's trichrome stain: 81-90
- c. Slide sequence number of iron stain:

d. Slide sequence number of other stain:

19. Are any stained slides to be returned to the clinic:



- 20. How many stained slides are to be returned to the clinic:
- 21. List sequence numbers of those slides to be returned
 - a. Slide sequence number:

81-90
81-90
81-90

c. Slide sequence number:

d. Slide sequence number:

b. Slide sequence number:

22. When do the stained slides need to be returned to the clinical center (check only one):

Immediately after central review At the end of the NASH CRN funding

(1)

period

2 of 3

23. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department

Other, (specify):

name
address
address
address

Note: this is the TONIC trial record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

phone

- G. Administrative information
 - **24.** Clinical Coordinator PIN: ____ ___
 - **25.** Clinical Coordinator signature:

Transfer Notification

Purpose: To record a transfer from one center to another center.

When: Upon transferring to the enrolling center and prior to the first visit at the adopting center.

By whom: Clinical coordinator of each center (enrolling center: sections A-C, adopting center: sections D-E).

Instruction: For enrolling center: When patient notifies enrolling center of upcoming transfer, the enrolling clinical coordinator should (1) complete Sections A-C of the Transfer Notification (TN Form), (2) send the TN form to the adopting center, with a copy of the most recent completed HI, LR, RD, and PE/PF forms, (3) send the labels for cryovials and slides and a copy of the visit window schedule to the adopting center. For adopting **center:** Prior to the patient coming to the adopting center, the adopting clinical coordinator should: (1) complete Sections D-E of the TN form, (2) Fax the TN form to the DCC (Fax: 410-955-0932). The DCC will key the form.

A. Enrolling center and par	tient iden	tification	l	13. Clinical coordinator signature:
1. Center ID:				
2. Patient ID:				D. Adopting center, patient and visit identification 14. Adopting center ID:
3. Patient code:	-			
4. Date of notification of i	ntent to tra	ansfer:		15. Patient ID (must be same as in Section A):
	mon	-	year	16. Patient code (must be same as in Section A):
5. Visit code:	-	<u>n</u>		
6. Form & revision:	_	<u>t</u> n	_1_	17. Expected date of first followup visit at adopting center:
7. Study:		TON	IC_3_	day mon year
B. Last followup visit infor	mation			18. Visit ID code for expected first followup visit at adopting center:
8. Date of last followup vi	sit:			_f
	mon	 =;	year	Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.
9. Visit ID code of last convisit:	mpleted fo	ollowup		E. Adopting center administrative information
	_f			19. Date form reviewed:
10. Have cryovial and slide to the adopting center:	labels bee	en sent		day mon year
* Send the cryovial and	(slide label	Yes 1) Is to the a	$\binom{N_0}{*_2}$ dopting	20. Clinical coordinator ID:
center.				21. Clinical coordinator signature:
C. Enrolling center admini	strative ir	nformati	on	
11. Date form reviewed:				Fax form to the DCC. The DCC will key the TN form.
day	mon		year	·
12. Clinical coordinator ID:	:			

NASH CRN Adult NAFLD Database 2 NASH CRN Pediatric NAFLD Database 2

CONFIDENTIAL: Not for Citation or Distribution

NAFLD Database 2 Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
BG	Baseline History
BP	Blood Processing for Plasma and Serum
BQ	Beverage Questionnaire (BEVQ-15)
CF	Continuation Form
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
CV	Cardiovascular Risk Factors
DR	Death Report
EN	Database 2 Enrollment
FR	FibroScan® Report
HC	Hepatocellular Carcinoma Report
HF	Liver Biopsy Histology Findings
HI	Follow-up Medical History
ΙE	Interim Event Report
IR	Liver Imaging Studies Report
LD	Lifetime Drinking History (Skinner)
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LT	Liver Tissue Banking
MV	Missed or Incomplete Visit
PE	Physical Examination
RC	Rescreen Form
RG	Registration
SD	Liver Biopsy Materials Documentation
TN	Transfer Notification

NAFLD Database 2 AD – Alcohol Use Disorders Identification Test (AUDIT)

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.

When: Screening visit t0.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and review completed forms.

Respondent: Patient age 12 or older.

Instructions: Flash Card #9, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator then should complete section B below.

A. Center, patient, and visit identification				B. Administrative information (To be completed by Clinical Coordinator after			
1.	Center ID:			survey is completed.)			
2.	Patient ID:			8.	How was the questionnaire compl	eted:	
3.	Patient code:				Self-administered by patient Interview with translator	$\begin{pmatrix} & & 1 \\ & & 2 \end{pmatrix}$	
4.	Date of visit (date patient completed the form):						
		 	year	9.	Clinical Coordinator a. PIN:		
5.	Visit code:	_to			b . Signature:		
6.	Form & revision:	<u>a</u> _	<u>d</u> 1	10.	Date form reviewed:		
7.	Study:	NAFLD Dat	cabase 2 <u>6</u>				
					day mon	year	

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below *(items 1-10 are for clinical center use only)*.

11. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times a month	Two to three times a week	Four or more times a week
	(1)	(2)	(3)	(4)

12. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more
(0)	(1)	(2)	$($ $_{3})$	(4)

13. How often do you have six or more drinks on one occasion?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	(4)

14. How often during the last year have you found that you were not able to stop drinking once you had started?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$

15. How often during the last year have you failed to do what was normally expected from you because of drinking?

Less than			Daily or	
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(1)	(2)	(3)	(4)

Patient ID:		

16.	How often during the last year have you needed a first drink in the morning to get yourself going
	after a heavy drinking session?

Less than			Dail	
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

17. How often during the last year have you had a feeling of guilt or remorse after drinking?

Less than				Daily or	
Never	monthly	Monthly	Weekly	almost daily	
(0	$\begin{pmatrix} & & 1 \end{pmatrix}$	(2)	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)	

18. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
(0)	$\begin{pmatrix} & & 1 \end{pmatrix}$	(2)	$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$	(4)

19. Have you or someone else been injured as a result of your drinking?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

20. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

21. Today's date:

Thank you for completing this questionnaire.

BG - Baseline History

Purpose : To collect baselin When : Visit t0.	e history information about the	e patient.		
	Coordinator, reviewed by Stud	ly Physician.		
agrees with the diagnosis the patient is ineligible ar data system; but the form	nation by interview and chart r , the patient is ineligible for the nd cannot enroll in the NAFLD	review. If cis checked for an item, and the physic NAFLD Database 2 Study. If sis checked for a Database 2 Study. The form should not be keyed as for other patients who started screening, but were	an ite to th	em, ne
to be ineligible.	_			
A. Center, visit, and pat	ient identification	9. If yes, characterize the liver disease(s) <i>(check all that apply)</i>		
1. Center ID:		a. Alcohol related liver disease:	(1)
2. Patient ID:		b. Viral hepatitis:	(1)
_, _ , _ , _ ,	<u> </u>	c. Alpha-1 antitrypsin deficiency:	(1)
3. Patient code:		d. Wilson's disease:	(1)
		e. Glycogen storage disease:	(1)
4. Visit date (date this for	orm is initiated):	f. Iron overload:	(1)
	mon year	g. Fatty liver disease (NAFLD, NASH):	(1)
·	, and the second	h. Type of liver disease unknown:	(1)
5. Visit code:	_t0	i. Other (specify):	(1)
6. Form & revision:	_bg2_	specify		
7. Study:	NAFLD Database 2 6			
B. Family history	<u>-</u>	10. Do/did any of the patient's first degree relatives (parent, brother, sister, child) have cirrhosis:		
8. Do/did any of the pat relatives (parent, brothave liver disease:		$\binom{\text{Yes}}{1}$	(¹	No 2
Did any of the most	(Yes 1)	11. If yes, is the cause of the cirrhosis NASH-related or unknown (cryptogenic): (Yes (1)		No 、
a. Did any of the pati relatives die from		(₁)	(2)
	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	12. Do any of the patient's first degree relatives (parent, brother, sister, child) have diabetes (Type 1 or Type 2):		
		Yes	(1)
		No	(2)
		Don't know	(3)
		13. Do any of the patient's first degree relatives (parent, brother, sister, child) have obesity:		
		Yes	(1)
		No	(2)
		Don't know	(3)

Patient		

14.	Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:			19. Does the patient have a liver biopsy done no more than 90 days prior to registration in the Database 2 Study that you want
	Yes	(1)	evaluated for the Database 2 Study (complete the Liver Biopsy Histology Findings (HF) and Liver
	No	(2)	Biopsy Materials Documentation (SD) forms for
	Don't know	(3)	this biopsy):
15	Do any of the nations's first degree			$\binom{\text{Yes}}{*}$ $\binom{\text{No}}{2}$
13.	Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood			*Blood drawn for specimen collection must be
	fat:			within 90 days of the biopsy.
	Yes	(1)	20 D (Cl' 1')
	No	(2)	20. Date of liver biopsy no more than 90 days prior to registration in Database 2
	Don't know	(3)	Study that you want evaluated:
C. I	NAFLD history			
16.	Date patient was first diagnosed with			day mon year
10.	fatty liver disease or NASH-related cirrhosis:			21. Will the patient have a biopsy during screening:
		_		$\binom{\text{Yes}}{*}_{1}$ $\binom{\text{No}}{2}$
	day mon y	/ear		
17.	NAFLD, NASH, or NASH-related (SD) forms for this biopsy. Blood draw for		*Complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy. Blood draw for banking should be done <u>prior</u> to the biopsy or 4 days	
	a. Symptoms for liver disease:	(1)	after the biopsy.
	b. Result of being evaluated for another illness:	(1)	22. Has the patient had a liver imaging study in the past 6 months:
	c. During a routine or insurance physical			$\begin{pmatrix} \text{Yes} & \text{No} \\ \begin{pmatrix} * \\ 1 \end{pmatrix} & \begin{pmatrix} \text{No} \\ 2 \end{pmatrix} \end{pmatrix}$
	examination:	(1)	$\binom{1}{1}$ $\binom{2}{2}$
	d. Blood donation:	(1)	*Complete the Liver Imaging Studies Report (IR) form.
	e. Other (specify):	(1)	jorni.
				D. Weight history
	specify			22. What was the nationt's hirthwaight:
40				23. What was the patient's birthweight:
18.	What procedures/tests supported this first diagnosis (check all that apply)			lbs oz
	a. Liver biopsy:	(1)	24. Review flashcard 11. Which (picture)
	b. Imaging studies (Ultrasound, CT, MRI).	: (1)	best describes your weight pattern over
	c. Elevated aminotransferases:	(1)	the past 5 years (check only one):
	d. Other (specify):	(1)	Up and down, up and down
	· - · · · · · · · · · · · · · · · · · ·	`	12	Up gradually (2)
	specify			Up sharply (gained a lot in a brief interval) $\binom{3}{3}$
				Down gradually (4)
				Down sharply (lost a lot in a brief interval) $\binom{5}{5}$
				No or minimal change ()

25. What is the patient's current weight (ask the patient for his/her weight):

lbs

35. Did the patient try to lose or gain weight:

26. What is the most the patient has ever weighed:

Gain weight Lose weight

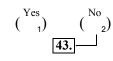
27. At what age did the patient weigh the

E. Tobacco cigarette smoking history (interview with patient; not interview with parent, not by chart review)

36. Which did the patient try to do (check only one):

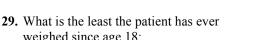
most:

37. Is the patient age 12 or older:



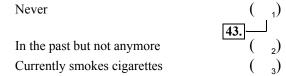
28. Is the patient age 18 or older:

38. Have you ever smoked tobacco cigarettes:



lbs

age in years



30. At what age did the patient weigh the

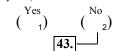
weighed since age 18:

least since age 18:

39. Did you smoke cigarettes regularly ("No" means less than 20 packs of cigarettes in a lifetime or less than I cigarette a day for one year):

age in years

lbs



years

years

31. Does the patient weigh more than he/she did one year ago:

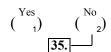
40. How old were you when you first started regular cigarette smoking:

32. How much more does the patient weigh now compared to one year ago:

41. How old were you when you (last) stopped smoking cigarettes (code as "n" if the patient didn't stop smoking):

33. Does the patient weigh less than he/she did one year ago:

42. On the average of the entire time that you smoked cigarettes, how many cigarettes



lbs

did you smoke per day:

34.	How much less does the patient weig	h
	now compared to one year ago:	

cigarettes/day

F. Menstrual history

43. Is the patient female:

Yes	No .
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	49.

44. Has menarche occurred:

(Ye	es 1)		(No (
	.,	49.	_	_ ً

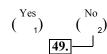
45. If yes, what was the patient's age at menarche:

age in years

46. Characterize the menstrual history in the past 5 years *(check only one):*

Regular periods	(1)
Irregular periods	(2)
Rare periods	(3)
No periods	(4)

47. Is patient post-menopausal:



48. What was the patient's age at menopause:

age in years

- G. Medical history (means Caution; condition is exclusionary if study physician agrees with diagnosis)
- **49.** Has the patient ever been diagnosed with and treated for any of the following (check all that apply; source of information can be interview and/or chart review)
 - **a.** Diabetes type 1:
 - **b.** Diabetes type 2:
 - **c.** Gestational diabetes (diabetes of pregnancy):
 - d. Hepatitis B:
 - e. Hepatitis C:

- **f.** Autoimmune hepatitis:
- g. Autoimmune cholestatic liver disorder (PBC or PSC):
- h. Wilson's disease:
- i. Alpha-1-antitrypsin (A1AT) deficiency: (1)
- j. Glycogen storage disease:
- k. Iron overload:
- **I.** Polycystic liver disease: (1)
- **m.** Drug induced liver disease:
- **n.** Gilbert's syndrome:
- **o.** Esophageal or gastric varices on endoscopy:
- **p.** Bleeding from varices: (1)
- **q.** Other gastrointestinal bleeding: (1)
- r. Ascites:
- s. Edema:
- t. Hepatic encephalopathy:
- 1)
- **u.** Portal hypertension:
- v. Hepatorenal syndrome: (1)
- **w.** Hepatopulmonary syndrome: (1)
- **x.** Short bowel syndrome:
- y. Hemophilia (bleeding disorder):
- z. HIV positive:
- aa. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:
- **ab.** Endocrine disease (hormonal abnormality): (1)
- ac. Hepatocellular carcinoma:
- ad. Other malignancy (cancer):
- **ae.** Peripheral neuropathy: (1)

	af. Seizure disorder or epilepsy:	(1)	51. Organ, limb, or bone marrow transplant
	ag. Drug allergies:	(1)	a. Has the patient ever received a liver
	ah. Hypothyroidism:	(1)	transplant: Yes
	ai. Hypertension:	(1)	$\binom{1}{1}$
	aj. Cerebrovascular disease:	(1)	b. Has the patient ever received any other organ, limb, or bone marrow
	ak. Dysbetalipoproteinemia:	<u>(c)</u>	(₁	transplant:
	al. Chronic cholestasis:	(1)	
	am. Hyperlipidemia (high cholesterol, high triglycerides):	(1)	52. Has the patient received total parenteral nutrition (TPN) for more than 1 month within 6 months prior to liver biopsy:
	an. Pancreatitis:	(1)	Yes
	ao. Cholelithiasis:	(1)	(₁)
	ap. Coronary artery disease:	(1)	
	aq. Elevated uric acid such as gout:	(1)	53. Is the patient currently undergoing
	ar. Kidney disease:	(1)	evaluation for bariatric surgery:
	as. Polycystic ovary syndrome:	(1)	$\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}$
	at. Sleep apnea (not breathing during sleep):	(1)	54. Does the patient have symptoms suggestive of sleep apnea <i>(snoring,</i>
	au. Dermatologic disorders:	(1)	observed periods of apnea, disruptive
	av. Myopathy:	(1)	sleep disturbances): Yes
	aw. Myositis:	(1)	(1)
	ax. Major depression:	(1)	
	ay. Schizophrenia:	(1)	
	az. Bipolar disorder:	(1)	
	ba. Obsessive compulsive disorder:	(1)	
	bb. Severe anxiety or personality disorder:	(1)	
	bc. None of the above:	(1)	
50.	Has the patient ever had surgery for an of the following (check all that apply)	у		
	a. Stapling or banding of the stomach:	<u>(c)</u>	₁)	
	b. Jejunoileal <i>(or other intestinal)</i> byp prior to the diagnosis of NAFLD:	ass (1)	
	c. Biliopancreatic diversion:	<u>(c)</u>	_1)	
	d. Other GI or bariatric surgery (specified)	fy): (1)	

e. None of the above:

(1)

H. Medication use

Glynase):

g. Insulin:

55. Has the patient used any antidiabetic medications in the past 3 months:

	$\binom{\text{res}}{1}$	(NO) 2)
	56.		
(If yes, check all that apply):			
a. Acarbose (Precose):		(1)
b. Acetohexamide (Dymelor):		(1)
c. Chlorpropamide (Diabinese):		(1)
d. Glimepiride (Amaryl):		(1)
e. Glipizide (Glucotrol, Glucotr	ol XL):	(1)
f. Glyburide (Micronase, DiaBe	eta.		

- **h.** Metformin (Glucophage, Glucophage XR): (
- i. Miglitol (Glycet): (j. Nateglinide (Starlix): (
- j. Nateglinide (Starlix):

 k. Pioglitazone (Actos):

 (1)
- I. Repaglinide (Prandin):
- **m.** Rosiglitazone (Avandia): $\binom{1}{1}$
- n. Tolazamide (Tolinase): (1)o. Tolbutamide (Orinase): (1)
- **p.** Other, (*specify*): (1)
- **56.** Has the patient taken any alcohol abuse (dependance or withdrawal) medications in the past 3 months:

Y	es		(^N	No ,
(1)		(2)
		57.		J

1)

(If yes, check all that apply):

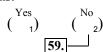
- **a.** Chlordiazepoxide (Librium): $\binom{1}{1}$
- **b.** Clorazepate dipotassium (Tranxene): (1)
- c. Diazepam (Valium): (1)
- **d.** Disulfiram (Antabuse):
- e. Hydroxyzine pamoate (Vistaril):
- **f.** Naltrexone hydrochloride (Revia): $\binom{1}{1}$
- **g.** Other, (specify): $\begin{pmatrix} 1 \end{pmatrix}$

57. Has the patient taken any antihyperlipidemic medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	58.

(If yes, check all that apply):

- **a.** Atorvastatin (Lipitor):
- **b.** Colestipol hydrochloride (Colestid): (
- **c.** Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)
- **d.** Gemfibrozil (Gen-Fibro, Lopid):
- e. Fenofibrate (Tricor):
- **f.** Fluvastatin sodium (Lescol): (1)
- g. Lovastatin (Mevacor):
- **h.** Nicotinic acid (Niaspan): (1)
- i. Pravastatin sodium (Pravachol):
- j. Rosuvastatin (Crestor):
- **k.** Simvastatin (Zocor):
- l. Other, (specify):
- **58.** Has the patient taken any antiobesity medications in the past 3 months:



(If yes, check all that apply):

- **a.** Dexfenfluramine hydrochloride (Redux):
- **b.** Fenfluramine hydrochloride (Pondimin):
- c. Methamphetamine hydrochloride (Desoxyn, Gradumet):
- d. Orlistat (Xenical):
- e. Phendimetrazine tartrate (Adipost, Bontril):
- **f.** Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
- g. Sibutramine hydrochloride monohydrate (Meridia):
- **h.** Other, (specify):

59. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 3 months:

Yes ()	(No
	60.	\square

(If yes, check all that apply):

- **a.** Acetaminophen (Tylenol): (1)
- **b.** Aspirin 325 mg: (
- **c.** Aspirin 81 mg: (₁)
- **d.** Celecoxib (Celebrex):
- e. Ibuprofen (Advil, Motrin):
- f. Indomethacin (Indocin):
- g. Naproxen (Aleve, Naprosyn):
- h. Rofecoxib (Vioxx):
- i. Other, (specify):
- **j.** Other, (specify): (1)
- **60.** Has the patient taken any strong opiates containing acetaminophen medication in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	61.

(If yes, check all that apply):

- **a.** Darvocet: (1)
- **b.** Esgic Plus: (1)
- c. Fioricet: (1)
- **d.** Lorcet:
- e. Lortab:
- **f.** Norco:
- g. Percocet:
- **h.** Talacen: () **i.** Tylenol #3: ()
- **j.** Tylenol #4:
- **k.** Tylox: (1)
- I. Vicodin:
- m. Wygesic:
- **n.** Other, (specify):

61. Has the patient taken any histamine H2 receptor antagonists/other gastrointestinal medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	62.

(If yes, check all that apply):

- **a.** Cimetidine (Tagamet):
- **b.** Esomeprazole magnesium (Nexium):
- c. Famotidine (Pepcid):
- **d.** Lansoprazole (Prevacid):
- e. Nizatidine (Axid):
- **f.** Omeprazole (Prilosec):
- g. Ranitidine (Zantac):
- **h.** Ranitidine bismuth citrate (Tritec):
- i. Antacids, (specify):
- **j.** Other, (specify):
- **62.** Has the patient taken any anticoagulant/antiplatelet medications in the past 3 months:

$$\begin{pmatrix}
\text{Yes} \\
\text{1}
\end{pmatrix} \qquad \begin{pmatrix}
\text{No} \\
\text{2}
\end{pmatrix}$$

(If yes, check all that apply):

- **a.** Clopidogrel (Plavix):
- **b.** Dipyridamole: (₁)
- c. Heparin:
- **d.** Ticlopide (Ticlid):
- e. Warfarin (Coumadin):
- **f.** Other, (specify):

63. Has the patient taken any systemic corticosteroids in the past 3 months:

j. Other, (specify):

Yes	1	۷o (
(1)	(2)
[6	54. —	J
(If yes, check all that apply):		
a. Betamethasone sodium (Celestone):	(1)
b. Cortisol:	(1)
c. Cortisone:	(1)
d. Dexamethasone (Decadron):	(1)
e. Hydrocortisone (Hydrocortone):	(1)
f. Methylprednisolone (Solu-Medrol):	(1)
g. Prednisolone (Prelone):	(1)
h. Prednisone:	(1)
i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort):	((ر

64. Has the patient taken any cardiovascular/antihypertensive medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	65.

(If yes, check all that apply):

- **a.** Amiodarone (Pacerone):
- **b.** Amlodipine besylate (Norvasc):
- c. Atenolol (Tenormin):
- **d.** Benazepril (Lotensin):
- e. Captopril (Capoten):
- **f.** Clonidine (Catapres):
- g. Digoxin (Lanoxin):
- **h.** Diltiazem (Cardizem):
- i. Doxazosin (Cardura):
- j. Enalapril (Vasotec):
- **k.** Felodipine (Plendil):
- **I.** Furosemide (Lasix):
- **m.** Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)
- **n.** Hydrochlorothiazide + triamterene (Dyazide): (1)
- o. Lisinopril (Prinivil, Zestril):
- **p.** Losartan potassium (Cozaar): (1)
- **q.** Losartan potassium with hydrochlorothiazide (Hyzaar): (1)
- r. Metoprolol (Lopressor):
- s. Nifedipine (Adalat, Procardia):
- **t.** Perhexiline maleate: (1)
- **u.** Propranolol (Inderal):
- v. Quinapril (Accupril):
- w. Terazosin (Hytrin):
- x. Timolol maleate (Blocadren):
- y. Valsartan (Diovan):
- **z.** Verapamil (Calan): (1)
- aa. Other, (specify):
- **ab.** Other, (specify):

1)

65. Has the patient taken any estrogen, progestin, hormone replacement therapy, or selective estrogen receptor modulators in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	66.

(If yes, check all that apply):

- a. Conjugated estrogen (Premarin/Prempro): (1)
- **b.** Diethylstilbestrol and methyltestosterone (Tylosterone):
- **c.** Esterified estrogen (Estratab, Menest): (1)
- **d.** Estradiol (Estrace): (1)
- **e.** Ethinyl estradiol (Estinyl): $\begin{pmatrix} 1 \end{pmatrix}$
- **f.** Fluoxymesterone (Android-F, Halotestin):
- **g.** Levonorgestrel (Norplant): (1)
- **h.** Medroxyprogesterone (Cycrin, Provera): (1)
- i. Megestrol (Megace):
- **j.** Methyltestosterone (Android): $\binom{1}{1}$
- **k.** Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): $\begin{pmatrix} & & & & \\ & & & & \end{pmatrix}$
- **l.** Norethindrone (Micronor):
- m. Norgestrel (Ovrette):
- **n.** Oral contraceptives: (1)
- o. Oxandrolone (Oxandrin):
- **q.** Progesterone (Prometrium): $\binom{1}{1}$
- r. Raloxifene (Evista): (1)
- s. Tamoxifen (Nolvadex):
- **t.** Other, (specify): (1)
- . Other, (*spectly)*.
- u. Other, (specify):

66. Has the patient taken any allergy or asthma medications in the past 3 months:

Yes	(No
(1)	(2)
	67.

(If yes, check all that apply):

- a. Beclomethasone dipropionate
 (Beclovent, Vanceril):

 ()
- **b.** Budesonide (Pulmicort, Rhinocort):
- **c.** Fluticasone propionate (Flonase, Flovent):
- **d.** Loratadine (Claritin):
- e. Mometasone furoate (Nasonex):
- **f.** Triamcinolone acetonide (Azmacort, Nasacort):
- **g.** Other, (specify):
- **h.** Other, (specify):
- **67.** Has the patient taken a multivitamin regularly in the past 3 months:

Yes	No
()	()
(1/	(2)

68. Has the patient taken vitamins other than multivitamins in the past 3 months:

(Y	es 1)		(¹	No
		70.		_

69. Which vitamins has the patient taken *(check all that apply)*:

c. Vitamin D:

- a. Vitamin B (any type):
- **b.** Vitamin C: (1)
- d. Vitamin E:
- e. Other, (specify):

70. Has the patient taken any supplements in the past 3 months:

	Yes	N	lo /
	(1)	71.	2 <i>)</i>]
(If yes, check all that apply):		/1.	
a. Alpha-lipoic acid:		(1)
b. Alpha-tocopherol:		(1)
c. Beta-carotene:		(1)
d. Betaine (Cystadane):		(1)
e. Calcium (any form):		(1)
f. Carnitine (any form):		(1)
g. Chondroitin (any form):		(1)
h. Choline + methionine + beta		,	,
adenosine + pyridoxine (Ep	ocler):	(1)
i. Cod liver oil:		(1)
j. Coenzyme Q:		(1)
k. Dichloroacetate:		(1)
I. Echinacea:		(1)
m. Fish oil (any form):		(1)
n. Flax seed oil:		(1)
o. Garlic:		(1)
p. Ginkgo biloba:		(1)
q. Glucosamine (any form):		(1)
r. Lecithin:		(1)
s. Magnesium:		(1)
t. Milk thistle:		(1)
u. N-acetyl-cysteine:		(1)
v. Potassium (any form):		(1)
w. S-adenylmethionine (SAM-	e):	(1)
x. Saw palmetto:		(1)
y. Selenium:		(1)
z. St. John's Wort:		(1)
aa. Taurine:		(1)
ab. Zinc picolinate:		(1)
ac. Other, (specify):		(1)

71. Has patient taken any of the following medications or other supplements/medications in the past 3 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	72.

(If yes, record all other supplements/medications):

- **a.** Demeclocycline (Declomycin): (1)
- **b.** Divalproex (Depakote): (1)
- c. Doxycycline (Monodox):
- **d.** Isotretinoin (Accutane):
- e. Levothyroxine (Levoxyl, Synthroid):
- **f.** Liothyronine (Cytomel):
- **g.** Methotrexate (Rheumatrex):
- **h.** Minocycline (Dynacin, Minocin):
- i. Oxytetracycline (Terramycin):
- 1. Oxytetracycline (Terramychi).
- j. Penicillamine (Cuprimine, Depen):

 k. Tetracycline (Achromycin):
- I. Trientine hydrochloride (Syprine):
- The state of the s
- **m.** Ursodeoxycholic acid (Actigall, Urso, Ursodiol):
- **n.** Valproate sodium (Depacon):
- **o.** Valproic acid (Depakene):
- **p.** Other, (specify):
- **q.** Other, (specify):
- r. Other, (specify):

ad. Other, (specify):

1)

Patient		
1 aucit	 	

I	Adn	niniet	rativa	a info	rmation

day

72. Study Physician PIN:
73. Study Physician signature:
74. Clinical Coordinator PIN:
75. Clinical Coordinator signature:
76. Date form reviewed:
76. Date form reviewed.

mon

year

NAFLD Database 2

BP - Blood Processing for Plasma and Serum

Purpose: Document collection of fasting blood for separation of plasma and serum.

When: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of blood.

Instructions: Blood must be collected, separated, and frozen on the same date. Label tubes of blood using MACO labels specific for the patient and visit; these labels are generated by the clinical center upon registration (screening visit labels) or after enrollment (follow-up visit labels). Attach duplicate blood tube labels in items 11 and 13. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Label 2.0 mL cryovials with numbered patient-specific plasma (blue-top) and serum (red-top) cryovial labels provided by the DCC. Affix plasma aliquot #00 label and serum aliquot #00 label to this form in item 18. If blood was collected for FLINT or CyNCh but patient was ineligible, transcribe data from the FLINT or CyNCh BP form, including the cryovial label information, and attach that form to the NAFLD Database 2 BP form.

Screening:

For plasma: Fill <u>one</u> 10 mL green top heparin tube with blood. Process blood for plasma within 30 minutes according to procedures specified in the NAFLD Database 2 SOP I. After separation, prepare up to 10 aliquots of plasma: pipette 0.5 mL of plasma to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of plasma at -70 C.

For serum: Fill <u>three</u> 10 mL SST red-gray top tubes with blood. Process blood for serum within two hours according to procedures specified in the NAFLD Database 2 SOP I section. After separation, prepare up to 30 aliquots of serum: pipette 0.5 mL of serum to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of serum at -70 C.

Follow-up visits:

For plasma: Fill <u>one</u> 10 mL green top heparin tube with blood. Process blood for plasma within 30 minutes according to procedures specified in the NAFLD Database 2 SOP I section. After separation, prepare up to 10 aliquots of plasma: pipette 0.5 mL of plasma to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of plasma at -70 C.

For serum: Fill <u>two</u> 10 mL SST red-gray top tubes with blood. Process blood for serum within two hours according to procedures specified in the NAFLD Database 2 SOP I section. After separation, prepare up to 20 aliquots of serum: pipette 0.5 mL of serum to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of serum at -70 C.

NOTE: Immediately upon completion of plasma and serum aliquot preparation, destroy any leftover cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be able to be determined.

A. Center, patient and visit identification		B. Processing whole blood Plasma and serum aliquots are to be	senarate
1. Center code:		from whole blood per instructions in t section. Draw fasting blood in the morn	he SOP
2. Patient ID:		8. Was participant fasting for at least 8 hours* prior to blood draw:	N-
3. Patient code:		$(\begin{array}{c} Yes \\ (\begin{array}{c} 1 \end{array})$ *12 hour fast is preferred.	(No.
4. Date of visit:		a. Was blood collected for the NIDDK Biosample Repository:	
	mon year	Yes	(1
5. Visit code:		Yes, collected for another study, but not used	(2
		No, (specify):	(* 3
6. Form & revision:	<u>b</u> <u>p</u> <u>3</u>		23.
7. Study: NA	FLD Database 2 6	specify reason	
-		*If patient did not come to clinic for	

Patient ID:	

	d	ay —	mon		year
b. T	hour	: minute	_	(₁)	(pm 2)
10. Nun	nber of he	parin (gree	n-top) t	ubes:	

NAFLD DB 2 Form,		
BP Plasma.		
Pt:	9999, xyz	
Visit	vvvv	
Date:		

- **12.** Number of SST serum separator (red-gray top) tubes:
- **13.** Attach duplicate SST serum separator tube labels *(only key NASH ID):*

NAFL	DDB 2 Serum 1
Pt:	9999, xyz
Visit:	vvvv
BP	
Date:	

NAFLD	DB 2 Serum 2
Pt:	9999, xyz
Visit:	VVVV
BP	
Date:	

*Needed during screening only

NAFL	D DB 2 Serum 3	*
Pt:	9999, xyz	
Visit:	VVVV	
BP		
Date: _		
1		

14.	Phlebotomist:		

print name

C. Aliquots for plasma and serum

Pipette 0.5 mL of plasma into each of up to ten 2.0 mL pre-labeled cryovials and pipette 0.5 mL of serum into each of up to 30 (screening); 20 (follow-up) 2.0 mL pre-labeled cryovials.

15. Time of separation into plasma and serum aliquots

a. Time of plasma separation:

	:	(1)	(,)
hour	minute	am	pm

b. Time of serum separation:

17. Number of aliquots for serum:

	hour	minute	(₁)	(pm
16. Nu	ımber of ali	quots for plasma	a:	

18. Attach duplicate cryovial labels (use aliquot #00 labels which are located in the first row of labels in the set):

Serum aliquot #00 label	Plasma aliquot #00 label

19. Technician:

print name

D. Freezing aliquots

Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK Biosample Repository at Fisher BioServices.

20. Time cryovials frozen in -70°C or -20°C

hour minute (1) (2)

21. Number of cryovials frozen: ____ __

E. Administrative information

- **23.** Clinical Coordinator PIN:
- 24. Clinical Coordinator signature:
- **25.** Date form reviewed:

NAFLD Database 2

BQ – Beverage Questionnaire (BEVQ-15)

Purpose: To obtain the patient's beverage intake.

When: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

By whom: Self-administered, but Clinical Coordinator must be available at visit to answer questions and to review completed form.

Respondent: Patient or completed by patient with parental assistance.

Instructions: The Clinical Coordinator should complete section A and attach a label to page 2 before giving the questionnaire to the patient for completion. The Clinical Coordinator should review the completed questionnaire for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to page 2 and the Clinical Coordinator should complete section C.

A. Ce	A. Center, patient, and visit identification			C. Administrative information (To be completed by clinical center staff after survey)				
1.	Center ID:			(To be completed by clinical center staff after survey is completed.)				
2.	Patient ID:			24. Clinical Coordinator PIN:				
3.	Patient code:			25. Clinical Coordinator signature:				
4.	Date of visit :							
	 day	mon	year	26. Date form reviewed:				
5.	Visit code:	t		day mon year				
6.	Form & revision:	<u> </u>	<u>q</u> 1					
7.	Study:	NAFLD Da	itabase 2 6					

B. Instructions: In the past month, please indicate your response for each beverage type by circling the best response for "how often" and "how much each time".

l)	1) Indicate how often you drank the following beverages, for	example, if you dra	ank 5 glasses of water
	per week, circle response "3" under the column labeled "4"	4-6 time per week'	,

2)	Indicate the approximate amount of beverage you drank each time, for example, you drank 1 cup
	of water each time, circle response "2" under the column labeled "8 fl oz (1 cup)" under "how much
	each time

3)	Do not count	beverages used	d in cooking	or other prepa	rations such	as milk in c	ereal

4) Count milk added to tea an	d coffee in the tea/coffee with	cream beverage category NOT	in the milk categories.

#		a.			b.								
				How of	ten <i>(circle</i>	one)			How much each time (circle one))
	Type of beverage	Never or less than 1 time per week (go to next beverage)	1 time per week	2-3 times per week	4-6 times per week	1 time per day	2+ times per day	3+ times per day	Less than 6 fl oz (3/4 cup)	8 fl oz (1 cup)	12 fl oz (1 ½ cups)	16 fl oz (2 cups)	More than 20 fl oz (2 ½ cups)
8.	Water	0	1	2	3	4	5	6	1	2	3	4	5
9.	100% Fruit Juice	0	1	2	3	4	5	6	1	2	3	4	5
10.	Sweetened Juice Beverage/ Drink (fruit ades, lemonade, punch, Sunny Delight)	0	1	2	3	4	5	6	1	2	3	4	5
11.	Whole Milk	0	1	2	3	4	5	6	1	2	3	4	5
12.	Reduced Fat Milk (2%)	0	1	2	3	4	5	6	1	2	3	4	5
13.	Low Fat/Fat Free Milk (Skim, 1%, Buttermilk, Soymilk)	0	1	2	3	4	5	6	1	2	3	4	5
14.	Soft Drinks, Regular	0	1	2	3	4	5	6	1	2	3	4	5
15.	Diet Soft Drinks/Artificially Sweetened Drinks (Crystal Light)	0	1	2	3	4	5	6	1	2	3	4	5
16.	Sweetened Tea	0	1	2	3	4	5	6	1	2	3	4	5
17.	Tea or Coffee, with cream and/or sugar (includes non-dairy creamer)	0	1	2	3	4	5	6	1	2	3	4	5
18.	Tea or Coffee, black, with/ without artificial sweetener (no cream or sugar)	0	1	2	3	4	5	6	1	2	3	4	5
19.	Beer, Ales, Wine Coolers, Non-alcoholic or Light Beer	0	1	2	3	4	5	6	1	2	3	4	5
20.	Hard Liquor (shots, rum tequila, etc.)	0	1	2	3	4	5	6	1	2	3	4	5
21.	Wine (red or white)	0	1	2	3	4	5	6	1	2	3	4	5
22.	Energy or Sport Drinks (Red Bull, Rockstar, Gatorade, Powerade, etc.)	0	1	2	3	4	5	6	1	2	3	4	5
23.	Other (specify):	0	1	2	3	4	5	6	1	2	3	4	5

Citation: Hedrick VE, Savla J, Comber DL, Flack KD, Estabrooks PA, Nsiah-Kumi PA, Ortmeier S, Davy BM. Development of a Brief Questionnaire to Assess Habitual Beverage Intake (BEVQ-15): Sugar-Sweetened Beverages and Total Beverage Energy Intake. J Acad Nutr Diet. 2012; 112:840-849.

Affix label here

Patient ID: Patient code: Visit code:

NAFLD Database 2

CF - Continuation Form

Purpose: (1) To identify and document the patients who consent to continue in the NAFLD Database 2 study, and (2) close out patients who, in the opinion of the clinical center, will not be good candidates for continuing in the next phase.

When: At the t192 or t240 visit.

Administered by: Clinical coordinator.

Respondent: None.

Instructions: Complete this form for each patient enrolled in the NAFLD Database 2 study at the t192 or t240 visit. A new visit window schedule for visits t240 through t480 will be generated upon keying this form for patients who are continuing in the NAFLD Database 2 study. If the patient does not consent to continue in the NAFLD Database 2 study, keying this form will close the patient out of the Database 2 study so that future visits will not be expected.

A. Center, patient, and visit identification	C. Administrative information			
1. Center ID:	10. Clinical Coordinator PIN:			
2. Patient ID:	11. Clinical Coordinator signature:			
3. Patient code:	12. Date form reviewed:			
4. Date of visit:	day mon year			
day mon year				
5. Visit code:t				
6. Form & revision:cf1				
7. Study: NAFLD Database 2 6				

B. Database 2 participation

8. This patient will continue in the NAFLD Database 2 study:

9. Has the patient or parent signed the latest version of the NAFLD Database 2 informed consent (if applicable):

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{*}_{2}$

^{*} Patient must sign the informed consent if required by local IRB

CG - Genetic Consent and Blood Collection Documentation NAFLD Database 2

Purpose: To document options selected for use of blood samples for genetic research.

When: Visit t0 or as needed during follow-up (during follow-up, use the visit code of the follow-up visit that is

By whom: Study Physician, Clinical Coordinator and laboratory personnel responsible for collection of blood. **Instructions**: Complete this form based on the consent documents signed by the patient/parent. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG form. If the patient consents, (1) Fill one 10 mL EDTA vacutainer tube with blood. (2) Pack and ship the blood in the EDTA tube to the NIDDK Genetics Repository at Rutgers University on the same day blood is collected. Ship at ambient room temperature. Ship blood in the specimen shippers supplied by the NIDDK Genetics Reposi-

A. Center, patient and visit identification						
1. Center ID:						
2. Patient ID:						
3. Patient code:						
4. Date form comp	oleted:					
day	<u> </u>	mon		y	ear	
5. Visit code:						
6. Form & revision	1:		_c_	_g_	_2	
7. Study:	NAFL	D Dat	abas	e 2	6	

- B. Consent for collection, storage, and use of blood samples for current and future genetic research
 - 8. Has a sufficient yield of DNA (≥100 micrograms) been banked at the NIDDK Genetics Repository for this participant in a previous NASH CRN study:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

20.

9. For which study was it collected (check all that apply):

a. Database	(1
b. PIVENS	(1
c. TONIC	(1
d. Other, (specify):	(1
specify		

10. Does the patient/parent consent to genetic research on NAFLD or NASH-related cirrhosis that is currently planned by the study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

11. Does the patient/parent consent to future genetic research on NAFLD or NASH-related cirrhosis by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

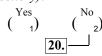
12. Does the patient/parent consent to future genetic research not related to NAFLD or NASH-related cirrhosis by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

13. Other information related to consent for genetic research that clinic staff feel needs to be keyed to the study database (e.g., if vour genetic consent had other options that are not covered by the 3 categories of use of samples *specified above):*

_			
-			
-			

14. In your judgment, has the patient/parent consented to collection of blood for DNA banking (this question is asked in recognition that not all IRBs will have approved consent statements that include language that can be mapped into the questions in items 10 through 12; a response of "No" to this question (item 14) means that blood should NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):



C. Specimen for Genetics Repository

Attach ID label to one 10mL EDTA tube and fill with blood; invert the tube gently 6 times to mix blood with additives; keep tube at room temperature until the same day shipment to the NIDDK Genetics Repository.

15. Was blood collected today for the NIDDK Genetics Repository:

Yes		(1)
No, (specify):		16. (₂)
	specify	
		20.

- 16. Date and time of blood draw
 - a. Date:

	day	mon	year
b. Time:			
	:	_ (,) (2)
hour	minute	am	pm

- **17.** Number of 10 mL EDTA tubes:
- **18.** Form copy of tube label:

NAFLD DB 2 Form CG Pt: ccc- 9999, xyz Gender Age, yrs.: XX

19. Phlebotomist:

print name

D	Δdm	inictr	ative	inform	nation
ν.	Aun	mmsu.	auve	IIIIVII	паиоп

- **20.** Study Physician PIN:
- **21.** Study Physician signature:
- **22.** Clinical Coordinator PIN:
- **23.** Clinical Coordinator signature:
- 24. Date form reviewed:

 day mon year

year

NAFLD Database 2

CO - Database Closeout

Purpose: To temporarily close out NAFLD Database 2 participation for a patient enrolled in the NAFLD Database 2 in order for the patient to be randomized in another NASH CRN study. Once this form is keyed, the patient is exempt from completing visits in the NAFLD Database 2.

When: Ideally, upon randomization of the NAFLD Database 2 patient into another NASH CRN study, but this form can be completed at any time. Use visit code n.

Administered by: Clinical coordinator.

Respondent: None.

Instructions: This form must be completed and keyed for patients enrolled in the NAFLD Database 2 who are subsequently randomized in FLINT, CyNCh, or other NASH CRN study. Until it is keyed, the patient will remain on the active patient list, meaning that all Database visits are due for the patient. The keying of this form will turn off the visit windows for the NAFLD Database 2. If the patient is not randomized in the new study, this form should not be keyed. If it has already been keyed, it should be deleted.

A. Center, patient, and visit identification	C. Administrative information
1. Center ID:	10. Clinical Coordinator PIN:
2. Patient ID:	11. Clinical Coordinator signature:
3. Patient code:	12. Date form reviewed:
4. Date of visit (date form is initiated; effective date for suspension of visit completion):	day mon
day mon year	
5. Visit code:n	
6. Form & revision: <u>c o 1</u>	
7. Study: NAFLD Database 2 6	
B. New study information	
8. Study that patient has been or will be randomized in <i>(check only one):</i>	
FLINT (1)	
CyNCh (2)	
Other (specify): (3)	
specify	
9. Date of randomization in new study (enter expected date if patient has not yet been randomized):	
day mon year	

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee.

By whom: Data Coordinating Center staff.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

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1 unem 1D
H & E stain
13. Steatosis (assume macro, e.g., large and small droplet)
a. Grade: 0 =<5%; 1 =5-33%; 2 =34-66%; 3 =>66%
b. Location: 0 =Zone 3 (central); 1 =Zone 1 (periportal); 2 =Azonal; 3 =Panacinar
c. Type of macrovesicular steatosis: 0 =Predominantly large droplet; 1 =Mixed large and small droplet;
2=Predominantly small droplet
d. Microvesicular steatosis, contiguous patches: 0 =Absent; 1 =Present
14. Inflammation
a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:
0 =0; 1 =<2 under 20x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag
d. Amount of portal, chronic inflammation: 0=None; 1=Mild; 2=More than mild
d. Fillodik of portal, elifolite ilitalililation. V Trolle, I Trilla, I Trolle than fillia
15. Liver cell injury
a. Ballooning: 0=None → GOTO Item 15d; 1=Few; 2=Many
b. Severe ballooning present: 0 =No; 1 =Yes
c. Classical balloon cells present: 0 =No; 1 =Yes
d. Acidophil bodies: 0 =Rare/absent; 1 =Many
f. Megamitochondria: 0 =Rare/absent; 1 =Many
16. Mallory-Denk bodies: 0 =Rare/absent; 1 =Many
18. Glycogenosis of hepatocytes: 0 =Not present; 1 =Focal, involving less than 50% of the hepatocytes; 2 =Diffuse,
involving greater than or equal to 50% of the hepatocytes
19. Masson's trichrome stain
a. Fibrosis stage: 0=None → GOTO Item 20; 1a=Mild, zone 3 perisinusoidal (requires trichrome);
1b =Moderate, zone 3, perisinusoidal (<i>does not require trichrome</i>); 1c =Portal/periportal only;
2 =Zone 3 and periportal, any combination; 3 =Bridging; 4 =Cirrhosis
b. Perisinusoidal fibrosis grade: 0 =No perisinusoidal fibrosis present; 1 =Perisinusoidal fibrosis present that
requires a Masson stain to identify; 2=Perisinusoidal fibrosis present that is visible on the H&E stain
c. Predominant location of fibrosis: 0 =More predominance around or between portal areas; 1 =No portal or
central predominance; 2 =More predominance around/between central veins
20. Iron stain
a. Hepatocellular iron grade: 0 =Absent or barely discernible, 40x → GOTO item 20c ;
1=Barely discernable granules, 20x; 2=Discrete granules resolved, 10x; 3=Discrete granules resolved, 4x;
4=Masses visible by naked eye
b. Hepatocellular iron distribution: 0=Periportal; 1=Periportal and midzonal; 2=Panacinar; 3=Zone 3 or azonal
c. Nonhepatocellular iron grade: 0=None → GOTO item 21; 1=Mild; 2=More than mild
d. Nonhepatocellular iron distribution: 0 =Large vessel endothelium only; 1 =Portal/fibrosis bands only, but
more than just in large vessel endothelium; 2=Intraparenchymal only; 3=Both portal and intraparenchymal
21. Is this steatohepatitis? 99 =Not NAFLD; 0 =NAFLD, not NASH; 1a =Suspicious/borderline/indeterminate: Zone
3 pattern; 1b =Suspicious/borderline/indeterminate: Zone 1, periportal pattern; 2 =Yes, definite
2 pattern, 22 Suspicious, cordennie, macteriniate. Zone 1, periportar pattern, 2 100, definite
25. Other comments:

NAFLD Database 2

Cardiovascular Risk Factors

Purpose: To determine a patient's need for referral for cholesterol management based on the Adult Treatment Panel III (ATP III) cholesterol guidelines.

When: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

Administered by: Clinic coordinator by interview with patient and medical chart review.

Respondent: Patient age 18 or older.

Instructions: Collect information by interview, chart review, and by transcribing data from the Database 2 Physical Examination (PE), Laboratory Results (LR), and Baseline (BG) or Follow-up (HI) Medical History forms. The anthropometric, blood pressure, and laboratory values reported on this form should be those collected at the same visit

Important: Key the CV form only after you have keyed the BG/HI, LR, and PE forms.

A. Center, patient, and	visit identification	12. Total cholesterol (from LR form):
1. Center ID:		${mg/dL}$
2. Patient ID:		If the patient has total cholesterol greater than 300 mg/dL, an IE form should be completed.
3. Patient code:		13. HDL cholesterol (from LR form):
4. Date of visit:		${\mathrm{mg/dL}}$
day		14. LDL cholesterol (from LR form)*:
5. Visit code:	_t	*Enter ''GT'' if LDL cannot be calculated due to high triglycerides.
6. Form & revision:	<u>c</u> <u>v</u> <u>1</u>	15 Dividences
7. Study:	NAFLD Database 2 <u>6</u>	15. Blood pressurea. Systolic blood pressure (from PE form):
B. Framingham Risk A	ssessment	mmHg
8. Was a lipid panel of	otained at this visit: $ \begin{pmatrix} Yes \\ 1 \end{pmatrix} $ $ \begin{pmatrix} No \\ 2 \end{pmatrix} $	b. Diastolic blood pressure (from PE form):
	21.	mmHg
9. Gender Male Female	(₁) (₂)	16. Are you currently being treated for high blood pressure with medicine prescribed by your doctor: (Yes (1) (No 2)
10. Age:11. Are you a current ci	garette smoker: $ \begin{pmatrix} Yes \\ 1 \end{pmatrix} $ $ \begin{pmatrix} No \\ 2 \end{pmatrix} $	relatives).
		$\binom{\text{Yes}}{1} \qquad \binom{\text{No}}{2}$

- 18. Framingham point scores (use the ATP III At-a-Glance Quick Desk Reference [NIH Publication No. 01-3305] on page 4 to record gender-specific scores based on the patient's risk factors. Circle "+" or "-" as appropriate. Key + # or #; if 0 for an item with +/-, key "+0" or "+00".)
 - a. Age score (based on item 10; if the patient's age is 18 or 19, use the 20-34 age range):

+/-	
	points

points

points

- **b.** Total cholesterol score (based on items 10 and 12):
- c. Smoking score (based on items 10 and 11):
- **d.** HDL score (based on item 13): +/
- e. Systolic blood pressure score (based on items 15a and 16):

 points
- **19.** Point total (*Add items 18a-e*): + / ______ points
- 20. Framingham risk of heart attack or dying of coronary heart disease in the next 10 years (using the ATP-III at-a-glance publication on page 4, use the point total [item 19] to convert into gender-specific 10 year risk):

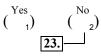
If 10 year risk % < 1, record "00". If 10 year risk $\% \ge 30$, record "30".

C. ATP III guidelines

21. Have you been diagnosed with type 1 or type 2 diabetes:

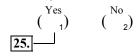
$$(Yes)$$
 (No)

22. Have you been diagnosed with clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

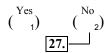


(If yes, check all that apply)

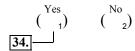
- a. Clinical CHD: (1)
- **b.** Symptomatic carotid artery disease: (
- **c.** Peripheral arterial disease:
- **d.** Abdominal aortic aneurysm:
- 23. Was "Yes" checked for either item 21 or 22 or was LDL unknown ("GT" in item 14 or lipid panel not obtained):



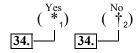
24. Is 10-year Framingham heart attack risk estimate 22% (item 20) or more:



25. Is LDL cholesterol (item 14) less than 100 mg/dL or was LDL unknown ("GT" in item 14 or lipid panel not obtained):



26. Is LDL cholesterol (item 14) 130 mg/dL or more:

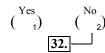


*Refer for cholesterol management with LDL-lowering drug therapy (see Database 2 SOP V).

†Refer for cholesterol management with drug therapy optional, initiate LDL-lowering therapeutic lifestyle changes (see Database 2 SOP V).

27.	Coronary heart disease (CHD) risk
	factors: Do you have any of the
	following:

- a. Current cigarette smoking (based on item 11):
- **b.** SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or on antihypertensive medication (based on items 15 and 16): (1)
- c. HDL cholesterol less than 40 mg/dL (based on item 13): (1)
- **d.** Family history of premature CHD (based on item 17):
- e. Age in men ≥ 45 years or age in women ≥ 55 years (based on items 9 and 10):
- **f.** HDL cholesterol 60 mg/dL or more (based on item 13):
- 28. Total number of CHD risk factors
 (add number of 'yes'' in items 27a-e and subtract 1 if item 27f is 'yes''; code as '0'' if only 27f is 'yes''):
- **29.** Are there 2 or more CHD risk factors (item 28):



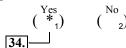
30. Is LDL cholesterol less than 130 mg/dL:

31. Is 10-year Framingham heart attack risk estimate between 10 and 20%, inclusive or LDL cholesterol 160 mg/dL or more:

*Refer for cholesterol management with LDL-lowering drug therapy (see Database 2 SOP V).

†Refer for cholesterol management with drug therapy optional, initiate LDL-lowering therapeutic lifestyle changes (see Database 2 SOP V).

32. Is LDL cholesterol 190 mg/dL or more:



*Refer for cholesterol management with LDL-lowering drug therapy (see Database 2 SOP V).

33.	Is LDL	cholesterol	between	160	and	189
	mg/dL,	inclusive:				

Yes	No
(\dagger_1)	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

†Refer for cholesterol management with drug therapy optional, initiate LDL-lowering therapeutic lifestyle changes (see Database 2 SOP V).

D. Other cardiovascular events

- **34.** Has the patient ever been diagnosed with or treated for any of the following *(check all that apply)*
 - **a.** Myocardial infarction: (1)
 - **b.** Angina: ()
 - c. Stroke:
 - **d.** Cerebrovascular disease:
 - e. Coronary artery disease:
 - **f.** Congestive heart failure: (,)
 - g. Peripheral vascular disease:
 - **h.** Other cardiovascular disease (specify): (1)

specify

i. None of the above:

E. Administrative information

- **35.** Study Physician PIN:
- **36.** Study Physician signature:
- **37.** Clinical Coordinator PIN: ____ ____
- **38.** Clinical Coordinator signature:

39. Date form reviewed:

day	mon	year

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total			Points		
Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
2 3 4 5	1
4	1
5	2 2 3 4 5
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total			Points		
Cholesterol [Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
Γ	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2 3
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

NAFLD Database 2

DR - Death Report

Purpose: To record the report of a patient's death.

When: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form whenever the clinical center is informed of a patient's death using as much information about the circumstances of death as possible. Fax a copy of the Death Report (DR) form, including the narrative, and the death certificate (if obtained) to the DCC at (410) 955-0932; Attention: Pat Belt. Also, complete an Interim Event (IE) form and follow the instructions to report a patient's death in the NAFLD Database 2. If either the cause or contributing cause of death is hepatocellular carcinoma (HCC), then also complete an Hepatocellular Carcinoma Report (HC) form.

A. Center, patient, a	nd visit identific	ation		10. Place and location of death		
1. Center ID:				a. Place of death (check only one):		
2. Patient ID:				Hospital	(1)
3. Patient code:				Hospice	(2)
		 -		Home	(3)
4. Date form is initial	ated (date of notic	ce):		Nursing home	(4)
day	mon	y	ear	Other (specify):	(5)
5. Visit code:	_n					
6. Form & revision:	_0	<u>l_r</u>	_2_	Unknown	(6)
7. Study:	NAFLD Data	base 2	_6_	b. Location of death:		07
B. Death information	n			city/state/country		
8. Date of death:	_	_		11. Has a death certificate been obtained: Yes	. [No 、
day	mon	ye	ear		(2)
9. Source of death re	eport (check all th	hat apply,) <i>:</i>	If no, please obtain or explain why not:		
a. Patient's famil	y:		$\begin{pmatrix} 1 \end{pmatrix}$			
b. Friend:			$\begin{pmatrix} 1 \end{pmatrix}$			
c. Other caregive	er:		$\begin{pmatrix} 1 \end{pmatrix}$			
d. Health care prostaff:	ovider or NASH	CRN	(1)			
e. Newspaper:			$\begin{pmatrix} 1 \end{pmatrix}$			
f. Funeral parlor/	home:		$\begin{pmatrix} 1 \end{pmatrix}$			
g. Medical record	d:		$\begin{pmatrix} 1 \end{pmatrix}$			
h. Medical exami	iner:		$\begin{pmatrix} 1 \end{pmatrix}$			
i. Coroner:			$\begin{pmatrix} 1 \end{pmatrix}$			
j. National Death	Index (NDI):		$\begin{pmatrix} 1 \end{pmatrix}$			
k. Social Security (SSDMF):	y Death Master F	ile	(1)			
I. Other (specify).	<i>:</i>		(1)			
	other source					
	other source					

12. Underlying cause of death (Study Physician: use whatever knowledge you have to best characterize the primary cause of death); (CHECK ONLY ONE):

Ulil.	
Coronary heart disease	(01)
Cardiovascular disease	13. (₀₂)
Liver disease	14. (₀₃)
Malignancy (cancer)	15. (₀₄)
Gastrointestinal (GI) disease	16. (₀₅)
Pulmonary (lung) disease	17.
Pneumonia	18.
Complication of diabetes	19. (₀₈)
Accident	19. (₀₉)
	19.
Suicide	19. — 10 <i>)</i>
Homicide	19. — 11)
Kidney disease or renal failure	(12)
Sepsis, staph or other infection	19. (₁₃)
Multi-organ failure	[19.] (₁₄)
Other (specify):	19. (₁₅)
	19.
Unknown	(16)
	19.

Patient I	D#:		
-----------	-----	--	--

13. CAUSE OF DEATH: Coronary heart disease (CHD) subclassification (*check only one*): Definite fatal myocardial infarction (MI) or heart attack $\begin{pmatrix} 1 \end{pmatrix}$ 1. Death within 28 days of hospital admission. OR 2. Postmortem findings consistent with MI within 28 days of hospital admission, OR 3. Documented definite or probable MI in previous 28 days if death occurred out of hospital and no evidence of a noncoronary cause of death, OR 4. Autopsy evidence of recent coronary occlusion or MI < 28 days old. Probable fatal MI 2) Defined as: 1. Death within 28 days of hospital admission in cases defined in probable MI cases, **OR** 2. Death within 6 hours of hospital admission with cardiac symptoms and/or signs. Other confirmatory data (biomarkers, ECG) are absent or not diagnostic). Definite fatal CHD $\begin{pmatrix} 3 \end{pmatrix}$ Defined as: 1. A history of CHD and/or documented cardiac pain within 72 hours before death and no evidence of a noncoronary cause of death, **OR** 2. Autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring. Go to 19. 14. CAUSE OF DEATH: Cardiovascular (CVD) disease subclassification (check only one): Congestive heart failure (CHF) 1) Defined as: Death due to clinical, radiologic or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock included). Documented arrhythmia Defined as: Death due to brady- or tachy- arrhythmias not associated with an acute ischemic event.

Defined as: Death due to stroke occurring within 7 days of signs and symptoms of stroke or during

Defined as: Death due to other known vascular diseases including abdominal aortic aneurysm rupture.

Go to 19.

Cerebrovascular (stroke)

admission for stroke.

Other cardiovascular

15. CAUSE OF DEATH: Liver disease subclassification <i>(check only one):</i>			18.	CAUSE OF DEATH: Pulmonary (lung) subclassification <i>(check only one)</i> :		
Nonalcoholic fatty liver disease				Asthma	(1)
$(NAFLD) \qquad ()$		Acute respiratory failure		(2)	
Chronic hepatitis C	(2)		Interstitial lung disease (ILD)	(3)
Acute liver failure	(3)		Other (specify):	(4)
Other (specify):	(4)			(4)
		 J	19.	Contributing causes of death (check all that apply):		
16. CAUSE OF DEATH: Malignancy (cancer) subclassification <i>(check only one)</i> :				a. Coronary heart disease (CHD) (specify):	. (1)
Breast cancer	(01)				
Colon cancer	(02)		b. Cerebrovascular disease (stroke):	(1)
Endometrial/Uterine cancer	(03)		c. Congestive heart failure (CHF):	(1)
Esophageal cancer	(04)		d. Documented arrhythmia, not		
Hepatocellular carcinoma (HCC)*	(05)		associated with MI:	(1)
* Complete and key the HC form.	,	``		e. Other cardiovascular disease (specify):	(1)
Ovarian cancer	(06)				
Pancreatic cancer	(07)		6 Disherter Town 1.	(`
Prostate cancer	(08)		f. Diabetes Type 1:	(1)
Rectal cancer	(09)		g. Diabetes Type 2:	(1)
Other known cancer or malignant tumor (specify):	(10)		h. Liver disease (specify):	(1)
Unknown cancer site	(11)		i. Hepatocellular (liver) carcinoma (HCC)*: * Complete and key the HC form.	(1)
17. CAUSE OF DEATH: Gastrointestinal subclassification (check only one):				j. Other malignancy (cancer) (specify):	(1)
Diverticular disease	()				
Clostridium difficile colitis	(1)		k. Gastrointestinal (GI) disease (specify):	(1)
Intestinal obstruction	((2 <i>)</i>		, , , , , , , , , , , , , , , , , , ,	,	12
Ulcer (gastric, duodenal, peptic,	(3)				
gastrojejunal)	(4)		l. Pulmonary (lung) disease (specify):	(1)
Vascular disorders of the intestine	(5)				
Other (specify):	(6)				
(*F = 327)	`	6/		m. Pneumonia:	(1)
				n. Kidney disease:	(1)
19		ا		o. Sepsis, staph or other infection:	(1)
19.		_		p. Other (specify):	(1)
				q. Unknown:	(<u>—</u> .)
				r. None:	(1))
				1. INOIRC.	1	1ノ

20.	Was this a procedure-related death:		
	Yes	(N	o (.
	22	, ,	2 <i>)</i>]
21.	Type of procedure-related death (check only one):	<u>'•</u>]	
	Cardiac death: Cardiovascular-related procedure (Defined as death after invasive cardiovalue intervention. Death within 28 days of vascular surgery or within 7 days of cath, arrhythmia ablation, angiovatherectomy, stent deployment, or oth sive coronary vascular intervention.):	cara card plas er in	lio- liac ty,
		(1)
	Cardiac death: Noncardiovascular procedure (Defined as cardiac death after noncacular intervention which occurs within of surgery or other invasive procedure	28 d	
	Non-cardiac death	(3)
	Unknown	(4)
22.	Was an autopsy performed (check only or	ne):	
	Yes	(1)
	No	(2)
	Unknown	(3)
23.	Documentation available for future formal death adjudication <i>(check all that</i>	apply) :
	a. Medical records documentation:	(1)
	b. Report of autopsy findings:	(1)
	c. Death certificate:	(1)
	d. ER record:	(1)
	e. EMS report:	(1)
	f. Informant interview:	(1)
	g. Coroner's report:	(1)
	h. Other (specify):	(1)
24.	Include a narrative from the Study Physician summarizing the event of death and comorbidities on page 6 and Fax a copy to the DCC ((410) 955-0932; Attention Pat Belt). Narrative is included Narrative is not included If not, please explain why not:	(1) 2)

25. Study Physician PIN:	
26. Study Physician signature:	
27. Clinical Coordinator PIN:	
28. Clinical Coordinator signature:	

C. Administrative information

29. Date form reviewed:		
	mon	year

Narr	rative - do not key:		

EN - Database 2 Enrollment

Purpose: • Check eligibility for NAFLD Database 2.

• Record reasons for ineligibility for patients found to be ineligible.

When: Visit t0.

Administered by: Study Physician (adult hepatologist or pediatrician) and Clinical Coordinator.

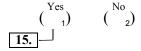
Respondent: Patient and Clinical Coordinator.

Instructions: If is checked for any item, complete the entire form but note that the patient may not continue in the NAFLD Database 2 study. If an item has not been assessed because the patient is ineligible, write "m" (missing) next to that item. This form should be keyed for each patient for whom a Registraition (RG) Form was completed without encountering a row.

A. Center, patient, and visit identification				
1. Center ID:				
2. Patient ID:				
3. Patient code:				
4. Visit date (date i	this form is initiated):			
day		year		
5. Visit code:	<u>t</u> 0			
6. Form & revision	<u>e</u> _	<u>n</u> _1_		
7. Study:	NAFLD Database	e 2 <u>6</u>		

B. Current status

8. Was participant previously enrolled in a NASH CRN study:



C. Alcohol use history consistent with NAFLD

9. On average, how many drinks containing alcohol has the patient had per week in the 2 years prior to screening:

Less than one drink a week	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
One drink a week	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
2 to 4 drinks a week	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
5 to 7 drinks a week	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$
8 to 10 drinks a week	(* 5)
11 to 14 drinks a week	(* 6)
15 or more drinks a week	\sim $($
	(Exig)—

^{*} Patient is ineligible if female

10. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient's alcohol use since starting the screening process consistent with NAFLD:

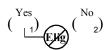


D. Exclusions

- **11.** Do any of the patient's assessments show evidence of these medical exclusions
 - **a.** Total parenteral nutrition (TPN) for >1 month within 6 months prior to liver biopsy:



b. Short bowel syndrome:



c. History of gastric or jejunoileal bypass prior to the diagnosis of NAFLD (bariatric surgery performed concomitant with or following the diagnosis of NAFLD is not exclusionary):



d. History of biliopancreatic diversion:



- 12. Child-Pugh Turcotte score
 - **a.** Serum albumin subscore (from Form LR: > 3.5 g/dL = 1, 2.8 3.5 = 2, < 2.8 = 3):
 - **b.** Serum total bilirubin subscore (from Form LR: < 2.0 mg/dL = 1, 2.0-3.0=2, > 3.0=3):
 - **c.** INR subscore (from Form LR: < 1.7=1, 1.7-2.3=2, > 2.3=3):

 1-3
 - d. Ascites subscore (use all available information from all sources to score; None=1, Mild, easily managed=2, Severe, refractory=3):

 1-3
 - e. Hepatic encephalopathy subscore

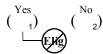
 (use all available information from
 all sources to score; None=1,
 Mild, easily managed=2,
 Severe, refractory=3):

 1-3

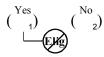
 - **g.** Evidence of advanced liver disease (*Child-Pugh-Turcotte score at least 10*):



- **13.** Do any of the patient's assessments show evidence of these medical exclusions
 - **a.** Evidence of chronic hepatitis B as marked by the presence of HBsAg in serum (patients with isolated anti-HBc are not excluded):



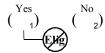
b. Evidence of chronic hepatitis C as marked by the presence of anti-HCV or HCV RNA in serum:



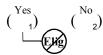
c. Low alpha-1-antitrypsin level and ZZ phenotype (*physician judgment*):



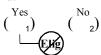
d. Wilson's disease:



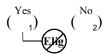
e. Known glycogen storage disease:



f. Known dysbetalipoproteinemia:



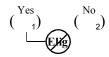
g. Known phenotypic hemochromatosis (removal of > 4 g of iron by phlebotomy in an individual 18 or older):



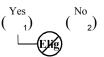
h. Congenital hepatic fibrosis or polycystic liver disease:



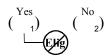
i. Other metabolic/congenital liver disease:



j. HIV infection or other systemic infectious disease:



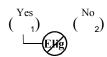
k. Disseminated or advanced extrahepatic malignancy:



l. Other severe systemic illness that in the opinion of the investigator would interfere with completion of followup:



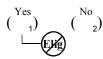
- 14. Do any of the patient's assessments show evidence of these histologic exclusions
 - **a.** Hepatic iron index > 1.9:



b. Prominent bile duct injury (florid duct lesions or periductal sclerosis) or bile duct paucity:



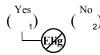
c. Chronic cholestasis:



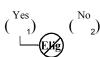
d. Vascular lesions (vasculitis, cardiac sclerosis, acute or chronic Budd-Chiari, hepatoportal sclerosis, peliosis):



e. Iron overload greater than 3+



f. Zones of confluent necrosis, infarction. massive or sub-massive, pan-acinar necrosis:



g. Multiple epithelioid granulomas:



15. Is there any other condition or issue that, in the opinion of the investigator, would interfere with the patient's adherence to study requirements:



- E. Check on plasma and serum collection and histologic criteria for inclusion in Database 2 study
- **16.** Date of plasma and serum collection:



- 17. Biopsy for NAFLD
 - a. Did participant have a biopsy for suspected or confirmed NAFLD within 90 days of plasma and serum collection (check "no" if local review shows cirrhosis):

Yes	(1)
No	(2
	18.

b. Date of biopsy:

_		_
day	mon	year

- **18.** Biopsy for NASH-related cirrhosis
 - a. Did participant have a biopsy for suspected or confirmed NASH-related cirrhosis within 90 days of plasma and serum collection:



b. Date of biopsy:

_		=
day	mon	year

F. Diagnostic category for inclusion

19. Diagnostic category for inclusion (use the most severe diagnosis from the HF form; i.e., if both NAFLD and cirrhosis are confirmed, check "2" for cirrhosis; check only one):

Biopsy for suspected or confirmed **NAFLD**

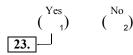
(item $17a = Yes$ and date in item $17b$ is		
within 90 days of date in item 16)	(1)

Biopsy for suspected or confirmed NASH-related cirrhosis (item 18a = Yes and date in item 18b is within 90 days of date in item 16)

Participant was previously enrolled in a NASH CRN study, but has not had a biopsy within past 3 months None of the above

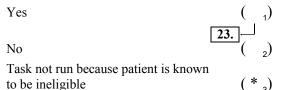
G. Eligibility check

20. Was an ineligibility condition checked or an eligibility not ascertained in items 9-15 or item 19:



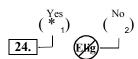
Instructions: Key visit t0 forms: RG and AD, BG, BP, CG, HF, LD, LR, LS, PE, as appropriate. Run the Enrollment Task on your clinic data system.

21. Were any STOP's or ineligible conditions other than "missing Form EN" identified by the Enrollment Task:



*You can skip running the Enrollment Task if you already know that the patient is ineligible; you must run the task to enroll the patient.

22. Does the patient/parent still consent/assent to enrollment (you should ask the patient/parent to orally affirm his/her consent/assent):



*Go to item 24 and complete this form. Then key this form and run the Enrollment Task on your clinic data system to enroll the patient.

H. Reasons for ineligibility for ineligible patients

NOTE: Complete this section for ineligible patients only.

- 23. Reason for ineligibility (check all that apply)
 - a. Reason covered in items 9-15, 19, or 22:
 - **b.** Tests are outside time window and clinic chose not to repeat tests:
 - c. Other reason not covered on this form (specify):

I. Administrative information

- **24.** Study Physician PIN:
- **25.** Study Physician signature:
- **26.** Clinical Coordinator PIN:
- **27.** Clinical Coordinator signature:
- **28.** Date form reviewed:

day	mon	year

FR - FibroScan® Report

NAFLD Database 2

Purpose: To record key data from the FibroScan[®] exam.

When: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

Administered by: NASH CRN certified FibroScan[®] technician(s) and Study Physician.

IMPORTANT: FibroScan[®] examinations may only be performed on NASH CRN patients. DO NOT perform on non-NASH CRN patients, per agreement with manufacturer.

Instructions: Verify that the patient has understood and signed the FibroScan consent form then file a copy in the patient records. Perform the exam per the procedures in the NAFLD Adult Database 2 SOP I. Briefly, this involves the following:

Before FibroScan examination, review the following information with patients: 1) Patients must have fasted for three or more hours prior to the FibroScan procedure (necessary medications are allowed with small amounts of water). 2) Clothing must permit access to the abdomen. 3) Check that the patient has no FibroScan contraindications (see item 9).

Instructions for keying data on FibroScan Touch Screen

1) On the FibroScan device, enter the patient ID (e.g., 9999) in the **LASTNAME** field; enter the letter code (e.g., zyx) in the **FIRSTNAME** field, and enter the visit code followed by NASH in the **CODE** field (e.g., t0 NASH). Enter NAFLD in the **ADMITTING DIAGNOSIS** field. Enter the PIN number of certified technician in the **OPERATOR** field.

Conduct of the two required FibroScan® procedures:

- 1) Emphasize the need to remain still during the procedure. 2) Position patient supine with right arm raised behind his/her head. 3) Apply a dime-sized amount of water based conduction gel over the liver. 4) Place M or XL probe over liver and obtain 10 valid measurements (if necessary, repeat until you have 10 valid measurements).
- 5) To choose between M and XL probe, follow the recommendation provided by the device. In case of recommendation fluctuating between M and XL, choose the XL. 6) Save test results, print test report, record results in Section D. 7) Repeat steps 2-6 above for second FibroScan exam. Each patient will have two exams. Reminder: Exam #2 may be performed by the same technician who completed Exam #1 or by a different certified technician.
- 8) Record results from the second exam in Section E.

A. Center, patient, and visit identification

1. Center ID:		
2. Patient ID:		
3. Patient code:		
4. Date form complete	ed (date of FibroSc	can [®] exam):
day	mon	year
5. Visit code:		
6. Form & revision:	<u>f</u> _	<u>r</u> 5
7. Study:	NAFLD Databa	ase 2 6

B. Consent

- 8. Has the patient signed the FibroScan® consent:

 Yes

 (* 2
 - * A FibroScan[®] exam should not be performed unless consent is obtained.
- **9.** Does the patient have any of the following contraindications (check all that apply):
 - **a.** An active implant such as pacemaker, defibrillator, pump, etc.: $\binom{}{}$
 - **b.** Wound near the site of scan: $\binom{1}{1}$
 - **c.** Pregnancy: (1)
 - **d.** Ascites (fluid in the abdomen):
 - **e.** Patient did not fast for 3 hours: $\binom{1}{2}$
 - **f.** Were any of the items above (a-e) checked:

Yes	No
(* 1)	(2)
21.	_
	6

* If any of the above are checked, the FibroScan[®] exam SHOULD NOT be performed. Skip to item 21.

C. FibroScan® Procedure information	n	E. F	ibroScan [®] exam #2 results	
10. Was FibroScan [®] exam performed:			(This may be done by the san	ne technician or a
Y			different technician).	
((es	17.	FibroScan® Technician PIN:	
12.	J			
* Complete item 11, then skip to it	em 21.	18.	Number of measurements	
11. Reason FibroScan® exam not perform (check all that apply):	ormed		a. Valid measurements*:	# of valid measurements
a. Patient had a skin-to-capsule dis measurement greater than 3.5cm			b. Invalid measurements:	# of invalid measurements
b. Other (specify):	(1)		c. Total measurements:	# of total measurements
Skip to item 21.			To calculate invalid measu valid measurements from total	
•			* Note: at least ten valid measu	arements should be
12. Probe type used:			made.	
M:	(1)	10	Equivalent Liver Stiffness (E)	
XL:	(2)	10.	a. Median (kPa):	•
D. FibroScan [®] exam #1 results			a. Median (Kra).	(1.5-75.0)
D. FibroScan exam #1 results			b. IQR (kPa):	•
13. FibroScan [®] Technician PIN:			b. Test (ki a).	
			c. IQR/med:	
14. Number of measurements				%
a. Valid measurements*:		20.	Controlled Attenuation Parame	ter (CAP)
•	# of valid measuremen	nts	a. Median (dB/m):	
b. Invalid measurements:				(100-400)
#	of invalid measureme	ents	b. IQR (dB/m):	
c. Total measurements:			Di iqir (az/m)	
	# of total measuremen		dministrative information	
To calculate invalid measuren valid measurements from total me		г. А	duministi ative inivi mativi	
* Note: at least ten valid measurer made.		21.	Study Physician PIN:	
		22.	Study Physician signature:	
15. Equivalent Liver Stiffness (E)				
a. Median (kPa):	<u> </u>			
	1.5-75.0)	23	Clinical Coordinator PIN:	
b. IQR (kPa):	<u> </u>	20.	omital coordinator ray.	
		24.	Clinical Coordinator signature:	
c. IQR/med:			· ·	
16. Controlled Attenuation Parameter	(CAP)	25	Date form reviewed:	
a. Median (dB/m):	(100,400)	~ U.		_
	(100-400)		day mon	year
b. IQR (dB/m):				

HC - Hepatocellular Carcinoma Report

Purpose: To record the report of a patient's diagnosis of hepatocellular carcinoma (HCC).

When: As soon as clinic is notified of a patient's diagnosis of HCC.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form whenever the clinical center is informed of a patient's diagnosis of HCC. Fax a copy of the Hepatocellular Carcinoma Report (HC) form to the DCC at (410) 955-0932; Attention: Pat Belt. Also, complete an Interim Event (IE) form to report a patient's HCC diagnosis in the NAFLD Database 2.

A. Center, patient, and	l visit identificati	on	12. Size of tumor (enter size of lan if more than one):	rgest tumor	
1. Center ID:			y more than one).		
2. Patient ID:			13. Was early enhancement presen	nt: Yes	No
3. Patient code:				(1)	(2)
4. Date form initiated	l (date of notice):		14. Was delayed washout present:	Yes	(No 2)
day	mon	year	15 W		(2)
5. Visit code:	_n	<u> </u>	15. Was serum marker alpha fetop (AFP) obtained:	Yes (1)	No
6. Form & revision:	_h_	_c_1_		(₁)	.]
7. Study:	NAFLD Databa	ase 2 <u>6</u>	a. Was serum AFP elevated:	Yes (1)	No No
B. Diagnosis informat	ion		b. Serum AFP level:		
8. Date of diagnosis:				999.9 ng/mL	
day	mon	year	C. Administrative information		
9. How was HCC ide	entified (check all	that apply):	16. Study Physician PIN:		
a. Ultrasound:b. CT scan:		$\begin{pmatrix} & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \end{pmatrix}$	17. Study Physician signature:		
c. MRI:d. Biopsy:		$\begin{pmatrix} & & 1 \\ & & 1 \end{pmatrix}$	10 Clinical Constitutes DDL		
e. Other (specify):		$\begin{pmatrix} 1 \\ 1 \end{pmatrix}$	18. Clinical Coordinator PIN:		
			19. Clinical Coordinator signature	: :	
10. Were results of im	aging obtained:		20. Date form reviewed:		

11. Were multiple tumors identified:

day

mon

year

HF - Liver Biopsy Histology Findings

Purpose: Record results of histologic evaluation of slides from screening liver biopsy.

When: Baseline visit t0 if liver biopsy slides are available and adequate for scoring.

By whom: Clinical Coordinator after Study Pathologist completes the Histology Worksheet (HW form).

Instructions: The Study Pathologist should complete the Histology Worksheet (HW) using the institution's H & E slide and if available, the institution's Masson's trichrome and iron slides. After completing the HW form, the Study Pathologist should give the worksheet to the Clinical Coordinator who will transcribe the data to the HF form and staple the worksheet to the HF form. Satellite centers should coordinate the scoring of the liver biopsy slides with the Study Pathologist at the parent center (see SOP I for the list of clinical centers and satellites). If is checked for an item, use caution; if the Study Physician agrees with the diagnosis, the patient is ineligible for the Database 2 and the form should not be keyed. If fewer than 2 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 2 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the DCC.

A. Center, patient and visit identification		C. NAFLD evaluation (use H & E and Masson's trichrome slides only)		
1. Center ID:		• ,		
A. D. C. A. ID.		10. Steatosis (assume macro, e.g., large and droplet)	nd sn	nall
2. Patient ID:		a. Grade:		
		< 5%	(0
3. Patient code:		5-33%	Ì	1)
		34-66%	Ì	2
4. Visit date:		> 66%	(3)
	year	b. Location:	`	0>
,	,	Zone 3	(0
5. Visit code:t0		Zone 1	(1)
		Azonal	(2)
6. Form & revision: <u>h</u> <u>f</u>	2	Panacinar	(3)
7. Study: NAFLD Database 2	2 6	11. Fibrosis stage (Masson's trichrome stain))	
,		0: None	(0
B. Biopsy information		1a: Zone 3, perisinusoidal (requires trichome)	(1)
8. Date this biopsy was performed <i>(obtaine surgical pathology report):</i>	ed from	1b: Zone 3, perisinusoidal (easily seen on H&E)	(2)
	year	1c: Portal/periportal only	(3)
a. Biopsy length:	<i>y</i> c	2: Zone 3 and periportal, any		
a. Biopsy length.	mm	combination	(4)
		3: Bridging	(₅)
9. What slides are to be used in this evaluation <i>(check all that apply)</i>		4: Cirrhosis	(6)
a. H & E:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$			
h Masson's trichrome:	()			

12. Inflammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

0	(0)	
< 2 / 20x mag	(1)	
2-4 / 20x mag	(2)	

b. Amount of portal, chronic inflammation:

> 4 / 20x mag

None to minimal	(0
Mild	(1)
More than mild	(ر (

13. Hepatocellular ballooning:

None	(0
Few	(1)
Many	(2)

14. Steatohepatitis diagnosis:

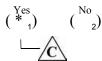
Not NAFLD	(0)
NAFLD, but not NASH	(1)
Suspicious/borderline/indeterminate, zone 3 pattern (1A)	3 (2)
Suspicious/borderline/indeterminate, zone li periportal pattern (1B)	l, (3)
Yes, definite steatohepatitis	(4)

D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

16. Is there evidence of Wilson's disease:



* Caution: Wilson's disease is exclusionary if the study physician agrees with diagnosis.

17.	Features	of chronic cholestatic liver	
	disease	(check all that apply):	

a. Bile duct loss/infiltration/sclerosis: (*	1.)

18. Features of other forms of chronic liver disease *(check all that apply):*

h Mana	(
h. None:	(. 1.

E. Evaluation of cryptogenic cirrhosis

19. Is cirrhosis present:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

20. In your opinion, is this **cryptogenic cirrhosis** (cirrhosis that fails to meet criteria for NAFLD and without evidence of other form(s) of chronic liver disease):

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

^{*} Caution: Exclusionary if the study physician agrees with diagnosis.

^{*} Caution: Exclusionary if the study physician agrees with diagnosis.

21. Other features <i>(check all that apply):</i>		
a. Mallory's hyaline (r/o cholate stasis):	(1)
b. Perisinusoidal fibrosis away from		
septa:	(1)
c. Hepatocyte ballooning:	(1)
d. Megamitochondria:	(1)
e. Other (specify):	(1)
f. None:	(1)
F. Other comments		
22. Other comments:		
G. Administrative information		
23. Study Pathologist PIN:		
24. Study Pathologist signature (Pathologist of need to sign this form if a signed HW attached.):		
25. Clinical Coordinator PIN:		
26. Clinical Coordinator signature:		
27. Date form reviewed:		
	vear	

HI - Follow-up Medical History

Purpose: To record follow-up medical history information about the patient. **When**: Visits t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480. **Administered by**: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview and chart review.

A. Center, visit, and patient identification

- **1.** Center ID: ____ _____
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- **4.** Visit date (date this form is initiated):

_		_
day	mon	year

- **5.** Visit code: __t__ _________
- **6.** Form & revision: _h_ i_ _1__
- 7. Study: NAFLD Database 2 6

B. Interval identification

8. Date of last Follow-up Medical History form (if this is visit t048 then date of t0):

day	mon	year

9. Visit code of last Follow-up Medical History form *(if this is visit t048 then t0):*

C. NAFLD evaluation

10. Has the participant had a liver biopsy since the last visit:

$$\binom{\text{Yes}}{*}$$
 $\binom{\text{No}}{2}$

*Complete the Liver Biopsy Materials Documentation (SD) form.

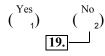
11. Has the participant had an upper abdominal imaging study since the last visit:

$$\binom{\text{Yes}}{*}$$
 $\binom{\text{No}}{2}$

*Complete a Liver Imaging Studies Report (IR) form.

D. Alcohol consumption (AUDIT-C) since the last visit

12. Is the patient age 12 or older:



13. Since the last visit, how often have you had a drink containing alcohol:

N	Never	(0
		16.	J
N	Monthly or less	(1)
Τ	Two to four times a month	(2)
Т	Two to three times a week	(3)
F	Four or more times a week	(₄)

14. Since the last visit, how many drinks containing alcohol have you had on a typical day when you are drinking:

15. Since the last visit, how often have you had six or more drinks on one occasion:

E. Tobacco cigarette smoking			r. Hepatic encephalopathy:	(1)
16. Since the last visit, have you smoked tobacco cigarettes regularly ("No" means			s. Portal hypertension:	(1)
			t. Hepatorenal syndrome:	(1)
smoked less than 1 day per week on averaş Yes		No	u. Hepatopulmonary syndrome:	(1)
$\binom{1}{1}$	(2)	v. Short bowel syndrome:	(1)
19.] —	J	w. Hemophilia (bleeding disorder):	(1)
17. On average, how many days per week have you smoked cigarettes:	_		x. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:	(1)
	# 0	days	y. Endocrine disease		
18. On the days that you smoked, about			(hormonal abnormality):	(1)
how many cigarettes did you smoke per day:			z. Hepatocellular carcinoma:	(1)
Par any.			aa. Other malignancy (cancer):	(1)
# cigarettes	ner d	Hav	ab. Peripheral neuropathy:	(1)
	pere	шу	ac. Seizure disorder or epilepsy:	(1)
F. Medical history			ad. Drug allergies:	(1)
19. Since the last visit, has the patient been			ae. Hypothyroidism:	(1)
diagnosed with or treated for any of the following (check all that apply; source of in	ıfor	ma-	af. Hypertension:	(1)
tion can be interview and/or chart review)	gori	iii d	ag. Cerebrovascular disease:	(1)
a. Diabetes type 1:	(1)	ah. Dysbetalipoproteinemia:	(1)
b. Diabetes type 2:	(1)	ai. Hyperlipidemia (high cholesterol, high triglycerides):	(1)
c. Gestational diabetes	(`	aj. Pancreatitis:	(1)
(diabetes of pregnancy):	(1)	ak. Cholelithiasis:	(1)
d. Hepatitis B:	(1)	al. Coronary artery disease:	(1)
e. Hepatitis C:	(1)	am. Elevated uric acid such as gout:	(1)
f. Autoimmune hepatitis:	(1)	an. Kidney disease:	(1)
g. Autoimmune cholestatic liver disorder (PBC or PSC):	()	ao. Polycystic ovary syndrome:	(1)
h. Wilson's disease:	(1) 1)	ap. Sleep apnea (not breathing during		
i. Alpha-1-antitrypsin (A1AT) deficiency:	(1)	sleep):	(1)
j. Iron overload:	$\dot{}$	`	aq. Dermatologic disorders:	(1)
k. Drug induced liver disease:	(1)	ar. Myopathy:	(1)
l. Gilbert's syndrome:	(1)	as. Myositis:	(1)
m. Esophageal or gastric varices on	(1)	at. Major depression:	(1)
endoscopy:	(1)	au. Schizophrenia:	(1)
n. Bleeding from varices:	(1)	av. Bipolar disorder:	(1)
o. Other gastrointestinal bleeding:	(1)	aw. Obsessive compulsive disorder:	(1)
p. Ascites:	(1)	ax. Severe anxiety or personality disorder:	(1)
q. Edema:	(1)	ay. None of the above:	(1)

20.	Since the last visit, has the patient had surgery for any of the following (check all that apply)		
	a. Stapling or banding of the stomach:	(1)
	b. Jejunoileal (or other intestinal) bypass:	(
	c. Biliopancreatic diversion:	(1)
	d. Other GI or bariatric surgery (specify):	(1)
	e. None:	(1)
21.	Since the last visit, has the patient received an organ, limb, or bone marrow transplant:		
	(Yes	(No 2
22.	Since the last visit, has the patient received total parenteral nutrition (TPN):		
	$\binom{\mathrm{Yes}}{1}$	(No 2
23.	Is the patient currently undergoing evaluation for bariatric surgery:		
	$\binom{\mathrm{Yes}}{1}$	(No 2)
24.	Since the last visit, has the patient been hospitalized:		
	$\binom{\operatorname{Yes}}{1}$	(No 2)
	25.		
	If Yes, specify reason:		
	specify reason		
25.	Since the last visit, has the patient had		
	any serious health problem not already reported:		
	Yes	, 1	No (

specify

G. Medication use

26. Since the last visit, has the patient used any antidiabetic medications (If yes, check all that apply)

	Yes	N	lo .
	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(2)
		27.	J
se (Precose):		(1)

- a. Acarbo
- **b.** Acetohexamide (Dymelor):
- c. Chlorpropamide (Diabinese): **d.** Glimepiride (Amaryl):
- e. Glipizide (Glucotrol, Glucatrol XL):
- f. Glyburide (Micronase, DiaBeta, Glynase):
- g. Insulin:
- h. Metformin (Glucophage, Glucophage XR):
- i. Miglitol (Glycet):
- **j.** Nateglinide (Starlix):
- **k.** Pioglitazone (Actos):
- **I.** Repaglinide (Prandin):
- m. Rosiglitazone (Avandia): n. Tolazamide (Tolinase):
- o. Tolbutamide (Orinase):
- **p.** Other, (specify):
- 27. Since the last visit, has the patient taken any alcohol abuse (dependance or withdrawal) medications:

If Yes, specify:

28. Since the last visit, has the patient taken any antihyperlipidemic medications (If yes, check all that apply)

Yes	No	
$\begin{pmatrix} 1 \end{pmatrix}$	(2	
	29.	

1)

- a. Atorvastatin (Lipitor):
- **b.** Colestipol hydrochloride (Colestid): (1)
- **c.** Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)
- **d.** Gemfibrozil (Gen-Fibro, Lopid): (1)
- e. Fenofibrate (Tricor):
- **f.** Fluvastatin sodium (Lescol): (
- **g.** Lovastatin (Mevacor):
- **h.** Nicotinic acid (Niaspan): $\binom{1}{1}$
- i. Pravastatin sodium (Pravachol): (1)
- j. Rosuvastatin (Crestor): (1)
 k. Simvastatin (Zocor): (1)
- **1.** Other, (specify): (1)
- **29.** Since the last visit, has the patient taken any antiobesity medications:

Y	es	N	lo
(1)	(2)

30. Since the last visit, has the patient taken any systemic corticosteroids:

Ŋ	/es	No	
(1)	(;	2

31. Since the last visit, has the patient taken any cardiovascular/antihypertensive medications (*If yes, check all that apply*)

		Yes (Yes	(No	2)
		3:	2.	
	/ T		1	`

- **a.** Amiodarone (Pacerone):
- **b.** Amlodipine besylate (Norvasc):
- c. Atenolol (Tenormin): (1)
 d. Benazepril (Lotensin): (1)
- e. Captopril (Capoten):
- **f.** Clonidine (Catapres):
- g. Digoxin (Lanoxin):
- **h.** Diltiazem (Cardizem):
- i. Doxazosin (Cardura):
- **j.** Enalapril (Vasotec):
- k. Felodipine (Plendil):
- **l.** Furosemide (Lasix): (₁) **m.** Hydrochlorothiazide (Esidrix,
- HydroDIURIL):
- **n.** Hydrochlorothiazide + triamterene (Dyazide): (1)
- **o.** Lisinopril (Prinivil, Zestril): (1)
- **p.** Losartan potassium (Cozaar): (1)
- **q.** Losartan potassium with hydrochlorothiazide (Hyzaar): (1)
- r. Metoprolol (Lopressor):
- s. Nifedipine (Adalat, Procardia):
- t. Perhexiline maleate: (1)
- u. Propranolol (Inderal):
- v. Quinapril (Accupril):
- w. Terazosin (Hytrin):

 x. Timolol maleate (Blocadren):

 (1)
- y. Valsartan (Diovan):
- z. Verapamil (Calan):
- aa. Other, (specify):
- ab. Other, (specify):

32. Since the last visit, has the patient taken any estrogen, progestin, hormone replacement therapy, or selective estrogen receptor modulators (*If yes, check all that apply*)

Yes (Yes	$\binom{\text{No}}{2}$
	33.

- **a.** Oral contraceptives:
- **b.** Raloxifene (Evista):
- c. Tamoxifen (Nolvadex):
- **d.** Other, (specify):

33. Since the last visit, has patient taken any of the following vitamins or supplements (*If yes, check all that apply*)

Yes	No
(100) (2)
	34.
a. MultiVitamin:	(1)
b. Vitamin B (any type):	(1)
c. Vitamin C:	(1)
d. Vitamin D:	(1)
e. Vitamin E:	(1)
f. Alpha-lipoic acid:	(1)
g. Alpha-tocopherol:	(1)
h. Beta-carotene:	(1)
i. Betaine (Cystadane):	(1)
j. Calcium (any form):	(1)
k. Carnitine (any form):	(1)
l. Choline + methionine + betaine +	
adenosine + pyridoxine (Epocler):	(1)
m. Cod liver oil:	(1)
n. Coenzyme Q:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
o. Echinacea:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
p. Fish oil (any form):	(1)
q. Flax seed oil:	(1)
r. Garlic:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
s. Ginkgo biloba:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
t. Glucosamine (any form):	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
u. Lecithin:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
v. Milk thistle:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
w. N-acetyl-cysteine:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
x. S-adenylmethionine (SAM-e):	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
y. Saw palmetto:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
z. Selenium:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
aa. St. John's Wort:	(1)
ab. Taurine:	(1)
ac. Zinc picolinate:	(1)
ad. Other, (specify):	(1)

34. Since the last visit, has patient taken any of the following medications or other supplements/medications (*If yes, check all that apply*)

Y	es	N	Jo ِ
(1)	(2)
	3	5. —	J

- a. Demeclocycline (Declomycin): (
- **b.** Divalproex (Depakote):
- **c.** Doxycycline (Monodox):
- **d.** Isotretinoin (Accutane):
- **e.** Levothyroxine (Levoxyl, Synthroid):
- f. Liothyronine (Cytomel):
- **g.** Methotrexate (Rheumatrex):
- **h.** Minocycline (Dynacin, Minocin):
- i. Oxytetracycline (Terramycin):
- **j.** Tetracycline (Achromycin): (1)
- **k.** Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (,)
- **l.** Valproate sodium (Depacon): (1)
- m. Valproic acid (Depakene): (1)
 n. Other, (specify): (1)
- o. Other, (specify):
- **35.** Since the last visit, has patient taken any pain relieving, non-steroidal anti-inflammatory, aspirin, or acetaminophen-containing medications:



H. Summary judgments about specific liver

conditions (these judgments are to be made after all of the visit data are collected)

- **36.** Subscores to compute Child-Pugh Turcotte score
 - a. Rate the patient's ascites (check only one):

None	-	(1)
Mild, easily managed		(2)
Severe, refractory		(3)

b. Rate the patient's hepatic encephalopathy *(check only one):*

None	(1)
Mild, easily managed	(2)

Severe, refractory (

	_			_		_
I. A	١dm	iinis	stra	tive	infor	·mation

- **37.** Study Physician PIN:
- **38.** Study Physician signature:
- **39.** Clinical Coordinator PIN:
- **40.** Clinical Coordinator signature:

41.	Date	form	reviewed:
41.	Date	torm	reviewed:

	_		_		
dav		mon		vear	

IE - Interim Event Report

Purpose: To document events that occur after registration that impact on the patient's participation in the NAFLD Database 2 Study (eg, mild or moderate liver biopsy complications). Complete this form if there has been an incident cirrhosis, hepatocellular carcinoma (HCC), hospitalization, Emergency Room visit, liver transplant, an event associated with a study-related procedure, or death.

When: As needed; use visit code n. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code n for first event, n1 for second event, etc.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 16) and the severity code (item 17) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at https://jhuccs1.us/nash/default.asp. Click on Documents and then click on General Documents. Fax the DCC (Attention: Pat Belt) a copy of this form if severity grade is 3 or higher (Fax 410-955- 0932).

NASH CRN Data Coordinating Center telephone number: (410) 955-8175.

A. Center, patient, and	l visit identificat	ion	C. Patient information			
1. Center ID:			9. Date enrolled in NAFLD Study (enter n if patient i		led):	
2. Patient ID:						
			day	mon	year	
3. Patient code:			10. Gender:			
4. Date of report:			Male		(1.
2. Date of report.			Female		(2,
day	mon	year	11. Age at time of event:			
5. Visit code:			11. Age at time of event.	_	years	
3. Visit code.	_n		D. Event description			
6. Form & revision:	_i_	e3_	12. Date event started:			
7. Study:	NAFLD Datal	pase 2 <u>6</u>			year	
3. Visit interval identi	fication		13. Nature of event (check al	l that apply)		
			a. General anesthesia		(1/
8. Most recently com or follow-up)	pleted visit (scree	ening	b. Study-related procedure	re:	(1/
a. Date:			c. Drug interactions:		(14
		_=	d. Worsening of a co-mo	rbid illness:	(1-
day	mon	year	e. Hypoglycemia:		(1.
b. Visit code:			f. New-onset diabetes:		(1
			g. Pregnancy (patient):		(1/
			h. Cirrhosis:		(1/
			i. Hepatocellular carcino. * Complete and key the	ma (HCC):	(*	: \ 1
			Complete and key the	: IIC 101 III.		

14. Did the event lead to (check all that apply,a. Emergency room visit:) (1)	18.		ent resolved if event is not	yet resolved):	
b. Hospitalization:	(1)					
c. Infectious episode:	(1)			day	mon	year
d. Surgical intervention:	(1)	19.	What ac	tion was taken	:	
15. Describe event:							
			90	Otheres	ammonts on our	onti	
			ZU.	Otner co	omments on eve	ent:	
16. Is the event listed in the NCIs Common							
Terminology Criteria for Adverse Events (CTCAE v3.0 document available at https://jhuccs1.us/nash/default.asp; click on Documents and then click on General							
Documents): ${{\operatorname{Yes}}\choose{{}^{1}}}$	(No 2)					
a. Indicate the name of the event (if in the CTCAE, specify name exactly from document; if not in CTCAE specify name):			F. A	dministr	ative informa	tion	
			21.	Clinical	Coordinator P	IN:	
			22.	Clinical	Coordinator si	gnature:	
17. Indicate the severity code using the CTCAE grading scale for the AE specified (severity grades are listed in the CTCAE v3.0 document availahttps://jhuccs1.us/nash/default.asp; c	b l e		23.	Study Pl	hysician PIN:		
Documents and then click on General ments):			2.4	Study Pl	nysician signat	iire.	
Grade 1 - Mild	(1)	~ 4.		J >===== 0.8.iut		
Grade 2 - Moderate	(2)					
Grade 3 - Severe†	(2' 3)	95	Data for	m reviewed:		
Grade 4 - Life threatening or disabling†	(4)	٤J.	Date 101	m ievieweu.		
Grade 5 - Death†	(* 5)			day	mon	year
† Fax the DCC (Attention Pat Belt) a copy of this form if severity grade is 3 or high		(Fax			s form and fax copy of this for		

Key this form and fax the DCC (Attention: Pat Belt) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious events so that we assure appropriate and timely study wide review. The received reports will be reviewed by Jeanne Clark, the Safety Officer, for appropriate further review by the Steering Committee and Data and Safety Monitoring Board.

410-955-0932).

*Complete and key Death Report (DR) form.

IR - Liver Imaging Studies Report

Purpose: To record liver imaging study results.

When: As needed during screening (visit t0) and follow-up (visits t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480).

Administered by: Clinical Coordinator.

Instructions: Complete this form at each of the visits listed above if the Baseline Medical History (BG) or Follow-up Medical History (HI) form says that a liver imaging study was obtained in the specified period. The form will allow you to skip out of sections that are irrelevant to your patient. What you will report at each visit are the results of the most recent scan of each type done in the 6 months prior to screening (visit t0) or in the period since the prior study visit (after enrollment). These will likely be standard of care scans with results obtained via medical records. In each case, answer the items based on review of the report; the Study Physician must review and approve the findings recorded on this form.

A. Center, patient, and visit identification 1. Center ID:	10. Findings suggestive of NAFLD, NASH-related cirrhosis, or others of significance <i>(check all that apply)</i>		
	a. Fatty infiltration:	(12
2. Patient ID:	b. Cirrhosis:	(12
3. Patient code:	c. Hepatomegaly:	(12
	d. Hepatic mass:	(12
4. Date of visit:	e. Intrahepatic biliary dilatation:	(1/
	f. Extrahepatic biliary dilatation:	(1/
day mon year	g. Gallstones/cholelithiasis:	(12
5. Visit code:	h. Gall bladder polyps:	(12
	i. Cholecystectomy:	(12
6. Form & revision:i _ r _ 1	j. Splenomegaly:	(12
7. Study: NAFLD Database 2 6	k. Ascites:	(12
	l. Other features of portal		•
B. Upper abdominal ultrasound	hypertension (specify):	(1
8. Did the patient have an upper abdominal ultrasound in the past 6 months (screening)/since the last visit (follow-up): Yes No 2	m. Other abnormality (specify):	(1.
9. Date of most recent upper abdominal ultrasound:	n. None of the above:	(12

C. Upper abdominal CT scan

11. Did the patient have an upper abdominal CT scan in the past 6 months (*screening*)/ since the last visit (*follow-up*):

(Y	es 1)	(ار (د
	•	14.	_ ل

12. Date of most recent upper abdominal CT scan:

day	mon	year
gs suggestive (of NAFLD,	

13. Findings suggestive of NAFLD, NASH-related cirrhosis, or others of significance (check all that apply)

a. Fatty infiltration:	(1)
b. Cirrhosis:	(1)
c. Hepatomegaly:	(1)
d. Hepatic mass:	(1)
e. Hepatic hemangioma:	(1)
f. Hepatic cyst:	(1)
g. Intrahepatic biliary dilatation:	(1)
h. Extrahepatic biliary dilatation:	(1)
i. Gallstones/cholelithiasis:	(1)
j. Gall bladder polyps:	(1)
k. Cholecystectomy:	(1)
l. Splenomegaly:	(1)
m. Ascites:	(1)

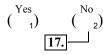
o. Other abnormality (specify): $\binom{1}{1}$

n. Other features of portal hypertension (*specify*):

n. None of the above:	(,

D. Upper abdominal MRI

14. Did the patient have an upper abdominal MRI in the past 6 months (*screening*)/ since the last visit (*follow-up*):



15. Date of most recent upper abdominal MRI:

		<u> </u>
day	mon	year

16. Findings suggestive of NAFLD, NASH-related cirrhosis, or others of significance *(check all that apply)*

f Hanatia areate

m. None of the above:

a. Fatty infiltration:	(1)
b. Cirrhosis:	(1)
c. Hepatomegaly:	(1)

d. Hepatic mass:	(1)
e. Hepatic hemangioma:	(1)

i. Hepatic cyst.	(1/
g. Intrahepatic biliary dilatation:	(1)

i. Spienomegary:	(1/
i Ascites:	()

k. Other features of portal		
hypertension (specify):	(1)

(1)

1)

1)

Patient ID:	 	

E. Ac	lminic	trative	infor	mation

day

17.	Study Physician PIN:
18.	Study Physician signature:
19.	Clinical Coordinator PIN:
20.	Clinical Coordinator signature:
21.	Date form reviewed:

mon

year

LD – Lifetime Drinking History (Skinner)

Keyed: ()

Purpose: To obtain quantitative indices of the patient's alcohol consumption patterns from the onset of regular drinking.

When: Visit t0. If more than one LD form is needed, use visit code "n" on the second LD form.

Administered by: Clinical Coordinator.

Respondent: New Database 2 Patients, 18 years of age or older, without help from spouse or family.

Instructions: Complete this form for new Database 2 patients only. In addition to actual consumption levels (quantity), attention is focused upon the frequency of use, variability in consumption, types of beverages, life events that mark a change in drinking pattern, solitary versus social drinking, and time of day when alcohol is consumed. Flash Card #9, Drink Equivalents, may be used with this interview.

The interviewer begins by recording the patient's alcohol consumption behavior during the first year that he/she drank on a regular basis (at least one drink per month). Then, the patient is asked to think of when his/her drinking behavior changed in any appreciable way. In a chronological fashion, the interviewer traces the patient's alcohol consumption behavior from the age of first regular drinking to the present. Flash Card #10, Patterns of Alcohol Intake, provides sample language for the interviewer. Each LD form allows for describing six drinking phases. Use a second LD form (visit code "n") if needed to describe additional drinking phases. If this is the second LD form, skip sections B and C and start with item 20.

The interview takes approximately 20 minutes to complete. It is best given after a reasonable degree of rapport has been established, whereby the patient will feel more at ease and talk openly. Other, considerable probing and cross-referencing of facts is necessary to help in accurate recall. All information should be recorded under the appropriate heading on the LD form.

Λ	Center	natient	and visit	identification
Α.	Center.	Dauent.	and visit	identification

1.	Center ID:				
2.	Patient ID:				
3.	Patient code:				
4.	Date of visit (date p	atient co	omplete	d the for	m):
		mon			ear
5.	Visit code:				
6.	Form & revision:		<u>l</u>	<u>d</u>	1
7.	Study:	NAF	LD Da	atabase	2 6

B. Lifetime alcohol consumption

8. Over the course of your lifetime have you ever had at least one drink of alcohol, beer, liquor, wine, or wine coolers, per month during a 12-month time period, or at least three drinks per day for at least three consecutive days (over a regular period of time):



Patient ID:		

C. First phase

Read as written: "Now, I am going to ask you about your drinking pattern during the first year that you began to have at least one drink per month until your drinking behavior was different in a significant way from this time."

9. How old were you when you began regular drinking:

a. Years:

yrs

b. Months:

mos

10. How old were you at the end of first stage:

a. Years:

yrs

b. Months:

mos

11. During the first stage, how many drinks would you have on average per occasion (*drinking day*):

drinks

12. How many days per month would you generally drink at this level:

days

13. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

14. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%):

Beer

%

Liquor

%

Wine

%

15. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent (1)
Occasional (less than 15 days) (2)

Weekend mainly (3 Binge (at least 3 days heavy drinking) (4

Frequent (15 days or more per month) (4)

16. Did any important event or events occur during this period that altered your usual drinking habits:

Yes No (1) (2)

17. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

Positive Negative Neutral Marital/family . . (2) 3) b. Work (1) 2) 3) School (c. 1) 2) 3) Medical (d. 1) 2) 3) e Residence (1) 2) f. Legal/jail (1) 2) Financial (g. 1) Peer group (h. 1) i. Drug abuse (3) 1) Treatment (j. 1) 2) 3) Death k. 1) 2) 3) Emotional

18. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%):

Alone

0/0

With others

<u>%</u>

Patient ID:		

19. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 %	
Afternoon	 %	
Evening	 0/.	

D. Subsequent phase

20. Read as written: "We have just discussed your drinking habits at the point when you first began to drink regularly. Now I want you to think to when your drinking behavior was different in a significant way from this time. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



21. How old were you at the beginning of this phase:

a.	Years:	
		yrs
b.	Months:	
		mos

22. How old were you at the end of this phase:

a.	Years:	yrs
b.	Months:	mos

23. During this phase, how many drinks would you have on average per occasion (*drinking day*):

		# drinks

24. How many days per month would you generally drink at this level (write "m" if not drinking):

# days	

25. What is the most or maximum number of drinks you would have in any one day:

#	drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

26. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

Beer	 %
Liquor	 %
Wine	 %

27. How would you rate your usual style of drinking during an average month *(check the appropriate category)*:

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	Ì	5)

28. Did any important event or events occur during this period that altered your usual drinking habits:



29. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

$c_{jj}cc$	<i></i>						
		Positi	ve	Nega	itive	Neu	tral
a.	Marital/family	(1)	(2)	(3)
b.	Work	(1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
g.	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse		1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
l.	Emotional	Ì	1)	į.	2)	Ì	₂)

Patient ID:		

30. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should		e time with at least one elative percentages of	35. During this phase, how many drinks would you have on average per occasion (<i>drinking day</i>):		
	add up to 100%; if not driv				# drinks
	should be "000"): Alone		36.	How many days per month we drink at this level (write "m	
		%			
	With others				# days
31.	During what time of the da of your drinking? Could y		37.	What is the most or maximu you would have in any one of	
	percentage of time during	the evening, afternoon			# drinks
	and morning (record the remorning, afternoon and evshould add up to 100%; if percentages should all be	ening; this section not drinking,		(Note: This is the maximum patient actually would drink his/her potential capacity.)	
	Morning				
	Afternoon	%	38.	What type of beverage woul consume in an average mont percentages of beer, liquor of	th (record the relative or wine; this section
		%		should add up to 100%; if no percentages should all be "(
	Evening	9/0		Beer	
E. Ne	xt subsequent phase			Beer	%
				Liquor	
32.	Read as written: "We have drinking habits when you regularly and at a subseque you to think to when your	first began to drink ent phase. Now I want		Wine	%
	different in a significant w phase. This could be the n perhaps 2 or 5 years later. events in your life that cha	ay from the previous lext 6 months or Can you think of any nged and may have	39.	How would you rate your us during an average month (checategory);	
	altered your drinking habit	Yes No (1) (2) (81.		Abstinent Occasional (less than 15 day Weekend mainly Binge (at least 3 days heavy	(3)
33.	How old were you at the b	eginning of the phase:		Frequent (15 days or more p	per month) (5)
	a. Years:	yrs			
	b . Months:	mos			
34.	How old were you at the e	nd of this phase:			
	a. Years:	yrs			
	b . Months:	mos			

40. Did any important event or events occur during this period that altered your usual drinking habits:

Y	es	N	No
(1)	(2)
	4	2. ◀	

41. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Neg	ative	Ne	utral
a.	Marital/family	. (1)	(2)	(3)
b.	Work	. (1)	(2)	(3)
c.	School	. (1)	(2)	(3)
d.	Medical	. (1)	(2)	(3)
e.	Residence	. (1)	(2)	(3)
f.	Legal/jail	. (1)	(2)	(3)
g.	Financial	. (1)	(2)	(3)
h.	Peer group	. (1)	(2)	(3)
i.	Drug abuse	. (1)	(2)	(3)
j.	Treatment	. (1)	(2)	(3)
k.	Death	. (1)	(2)	(3)
l.	Emotional	. (1)	(2)	(3)

42. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):

Alone	
With others	

43. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 %	
Afternoon	 %	
Evening	 %	

F. Next subsequent phase

44. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



45. How old were you at the beginning of the phase:

a.	Years:	
		yrs

- **b**. Months:
- **46.** How old were you at the end of this phase:

a.	Years:		
		yrs	

- **b**. Months:
- **47.** During this phase, how many drinks would you have on average per occasion (*drinking day*):

# drinks	

48. How many days per month would you generally drink at this level (write "m" if not drinking):

# days	

49. What is the most or maximum number of drinks you would have in any one day:

#	drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

Patient ID:		

50.	What type of beverage would you usually		
	consume in an average month (record the relative		
	percentages of beer, liquor or wine; this section		
	should add up to 100%; if not drinking,		
	percentages should all be "000"):		

Beer	 %	
Liquor	 %	
Wine	 0/0	

51. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent	(1
Occasional (less than 15 days)	(2
Weekend mainly	(3
Binge (at least 3 days heavy drinking)	(4
Frequent (15 days or more per month)	(5

52. Did any important event or events occur during this period that altered your usual drinking habits:



53. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Neg	ative	Ne	utral
a.	Marital/family .	. (1)	(2)	(3)
b.	Work	. (1)	(2)	(3)
c.	School	. (1)	(2)	(3)
d.	Medical	. (1)	(2)	(3)
e.	Residence	. (1)	(2)	(3)
f.	Legal/jail	. (1)	(2)	(3)
\mathbf{g} .	Financial	. (1)	(2)	(3)
h.	Peer group	. (1)	(2)	(3)
i.	Drug abuse	. (1)	(2)	(3)
j.	Treatment	. (1)	(2)	(3)
k.	Death	. (1)	(2)	(3)
l.	Emotional	. (1)	(2)	(3)

54.	What percentage of time would you drink alone,
	and what percentage of the time with at least one
	other person (record the relative percentages of
	"Alone" and "With others"; this section should
	add up to 100%; if not drinking, percentages
	should be "000"):

Alone	 %	
With others	 %	

55. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	%
Afternoon	
Evening	9/0

G. Next subsequent phase

66. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



57. How old were you at the beginning of the phase:

a.	Years:	
		yrs
b.	Months:	
		mos

58. How old were you at the end of this phase:

a.	Years:	
		yrs
b.	Months:	
		mos

Patient ID:		

59.60.	During this phase, how many drinks would you have on average per occasion (drinking day): # drinks How many days per month would you generally	65.	What was your perception of this event? Woul you say that it had a positive (desirable), negati (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):	ive e or	
	drink at this level (write "m" if not drinking):		ejjecij.		
61.	# days What is the most or maximum number of drinks		Positive Negative Net a. Marital/family . (1) (2) (b. Work (1) (2) (c. School (1) (2) (d. Medical (1) (2) (utral 3) 3) 3) 3)	
	you would have in any one day: # drinks		e. Residence (1) (2) (f. Legal/jail (1) (2) (g. Financial (1) (2) (3) 3) 3)	
	(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)		h. Peer group (1) (2) (i. Drug abuse (1) (2) (j. Treatment (1) (2) (k. Death (1) (2) (l. Emotional (1) (2) (3) 3) 3) 3) 3)	
62.	What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"): Beer	66.	What percentage of time would you drink alone and what percentage of the time with at least or other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"): Alone	ne of	
	Liquor				
	Wine		With others		
63.	How would you rate your usual style of drinking during an average month (check the appropriate category); Abstinent (1)	67.	of your drinking? Could you give me the percentage of time during the evening, afternous and morning (record the relative percentages morning, afternoon and evening; this section should add up to 100%; if not drinking,		
	Occasional (less than 15 days) Weekend mainly Binge (at least 3 days heavy drinking) Frequent (15 days or more per month) (2) (3) (4)		percentages should all be "000"): Morning		
64.	Did any important event or events occur during this period that altered your usual drinking habits:		Afternoon		
	Yes No (1) (2) 66.		Evening		

H. Next subsequent phase

68. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":

Yes No

69. How old were you at the beginning of the phase:

a. Years:

yrs

b. Months:

mos

70. How old were you at the end of this phase:

a. Years:

yrs

b. Months:

mos

71. During this phase, how many drinks would you have on average per occasion (*drinking day*):

drinks

72. How many days per month would you generally drink at this level (write "m" if not drinking):

days

73. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

74. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

75. How would you rate your usual style of drinking during an average month *(check the appropriate)*

Wine

category);

Abstinent (1)
Occasional (less than 15 days) (2)
Weekend mainly (3)
Binge (at least 3 days heavy drinking) (4)
Frequent (15 days or more per month) (5)

76. Did any important event or events occur during this period that altered your usual drinking habits:



77. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Positi	ve	Nega	ative	Neı	ıtral
a.	Marital/family	(1)	(2)	(3)
b.	Work	(1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
\mathbf{g} .	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse	(1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
l.	Emotional	(1)	(2)	(3)

Patient ID:		

78.	What percentage of and what percentage other person (record "Alone" and "With add up to 100%; if n should all be "000")	of the ting the relate others"; ot drinking	ne with ive perc this sect	at least o entages o ion shou	one of
	Alone	-			
				%	
	With others	-		%	
79.	During what time of of your drinking? Copercentage of time dand morning (record morning, afternoon a should add up to 100 percentages should of	ould you uring the lather the relate and eventions, if note	give me evening tive perc ing; this t drinkin	the g, afterno entages section	on
	Morning	-		<u>%</u>	
	Afternoon	-		% ————————————————————————————————————	
	Evening	-		%	
I. Nu	mber of phases				
80.	Are there any addition	onal subs	Ye		Jo 2)
	* If yes, complete a s Skip sections B and				
J. Adr	ministrative informat	tion			
81.	Clinical Coordinator	PIN:			
82.	Clinical Coordinator	signatur	e:		
83.	Date form reviewed:				
		mon		year	

LR - Laboratory Results - Tests Done During Screening and Follow-up

Purpose: To record archival and current laboratory test results for tests done during both screening and follow-up. **When**: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

Administered by: Study Physician and Clinical Coordinator.

Instructions: All laboratory test results are required during screening. Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversion or how to record a value. Staple the lab report to the back of this form. If your lab reports values electronically, print a copy of the results and staple the report to the back of this form.

A. Center, patient, and visit identification	12. Blood cell count
1. Center ID:	a. White blood cell count (WBC):
2. Patient ID:	10^{3} cells/ μ L or 10^{9} cells/L b. Red blood cell count (RBC):
3. Patient code:	$-$ mill cells/ μL
4. Date of visit (date form was initiated):	13. Platelet count:
day mon year	,,
5. Visit code:t	C. Chemistries and HbA1c
6. Form & revision:	14. Date of blood draw for chemistries:
 7. Study: NAFLD Database 2 6 B. Hematology 8. Date of blood draw for complete blood 	day mon year Date must be within the required time window; within 90 days of screening or in the time window for the follow-up visit (check the patient's Database 2 visit time window guide).
count: day mon year	15. Blood urea nitrogen (BUN):mg/dL
day mon year Date must be within the required time window; within 90 days of screening or in the time window for the follow-up visit (check the patient's Data-	16. Creatinine:
base 2 visit time window guide).	17. Uric acid:
9. Hemoglobin:	18. Date of blood draw for HbA1c:
10. Hematocrit:	day mon year Date must be within the required time window; within 90 days of screening or in the time window for the follow-up visit (check the patient's Database 2 visit time window guide).
	19. HbA1c:

D. Liver panel

20. Date of blood draw for liver panel:

		_=
day	mon	year

Date must be within the required time window; within 90 days of screening or in the time window for the follow-up visit (check the patient's Database 2 visit time window guide).

- **21.** Bilirubin (total): ____ _ _ _ _ _ _ _ _ _
- 22. Bilirubin (direct):
- 23. Aspartate aminotransferase (AST)

. Upper limit of normal:	
rr	U/L

24. Alanine aminotransferase (ALT)

	U/L
a. Upper limit of normal:	U/L

- 25. Alkaline phosphatase _______U/L
- **26.** Gamma glutamyl transferase (GGT):

U/L	

- 27. Total protein:
- **28.** Albumin: _____ ____ ____
- **30.** International normalized ratio (INR):

•	

E. Fasting lipid profile

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw.

31. Was participant fasting for at least 8 hours prior to blood draw:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

*12 hour fasting is preferred, but will accept nonfasting lipid values.

32. Date of blood draw for lipid profile:

=		=
day	mon	year

Date must be within the required time window; within 90 days of screening or in the time window for the follow-up visit (check the patient's Database 2 visit time window guide).

a. Triglycerides:	
	mg/dL

*Enter "GT" if LDL cannot be calculated due to high triglycerides.

F. Fasting glucose and insulin

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw. These tests are required during screening.

33. Was participant fasting for at least 8 hours prior to blood draw:

$$\binom{\text{Yes}}{1} \qquad \binom{\binom{\text{No}}{*}}{2}$$

*Patient must be fasting; 12 hour fast is preferred.

34.	Date of blood draw for fas and insulin levels:	sting g	glucos	e
	day Date must be within the within 90 days of screenin for the follow-up visit (ch base 2 visit time window cose and insulin value sho same blood draw.	ig or i leck th guide	n the t he pat). The	ime window ient's Data- e serum glu-
	a. Serum glucose:b. Serum insulin:		μU/mL	mg/dL •
G. A	dministrative informatio	n		
35.	Study Physician PIN:			
36.	Study Physician signature	:		
37.	Clinical Coordinator PIN:			
38.	Clinical Coordinator signa	ature:		
39.	Date form reviewed:			
	day	mon		year

LS - Laboratory Results -Tests Done only During Screening

Purpose: To record archival and current results of laboratory tests done only during screening.

When: Visit t0.

Administered by: Study Physician (adult hepatologist or pediatrician) and Clinical Coordinator.

Instructions:

New Database 2 patients: All laboratory test results are required at screening.

<u>Continuing Database 2 patients</u>: Laboratory tests may be repeated if clinically indicated.

Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have questions about conversion or how to record a value. Staple the lab report to the back of this form. If your lab reports values electronically, print a copy of the results and staple the report to the back of this form. If is checked for any item, you do not need to complete the rest of the form and the form should not be keyed.

A.	Center.	patient.	and	visit	identification

- **3.** Patient code: ____ ___
- **5.** Visit code: __t__0_______
- 7. Study: NAFLD Database 2 6
- **8.** Is the patient a continuing participant from Database, PIVENS, or TONIC:

$$\binom{\text{Yes}}{1} \qquad \binom{\binom{\text{No}}{*}}{2}$$

*All laboratory test results are required during screening.

9. Are new laboratory results available for the continuing participant:

*Record the date of blood draw as "m" if a test was not done.

B. Screening etiologic tests

10. Date of blood draw for serological assays to exclude viral causes of chronic liver disease:

day mon year

Repeat if date is greater than 5 years prior to screening.

If the patient is judged by Study Physician to have a high-risk lifestyle, repeat if date is greater than 6 months prior to screening.

a. Hepatitis B surface antigen (HBsAg): Positive



Negative
Hepatitis B core total a

b. Hepatitis B core total antibody (anti-HBc) (if total anti-HBc is not available, record results from IgG test):

Positive (1)

Negative (2

Not available (3.

c. Hepatitis B surface antibody (anti-HBs):

Positive (

Negative (2)

Not available (3)

d. Hepatitis C antibody (anti-HCV) (indicate result as negative if EIA is positive but RIBA is negative or if RIBA is indeterminate but HCV RNA is negative):

Positive

Negative (2

Δ	Hepatitis	C	virus	RNΔ
е.	перания	C	viius	MINA

Positive



Negative Not available

(2)
((ر

f. Hepatitis A virus antibody (anti-HAV, total):

Positive	(1)
Negative	(2)
		`

Not available (

C. Iron

11. Date of blood draw for iron overload screening:

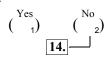
day	mon		year	
Repeat if date is greater	than	5 years	prior	to
screening.				

a. Iron:

μg/dL	

 ng/mL	

12. Is hepatic iron index available:

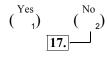


13. Hepatic iron index:



D. HFE gene analysis

14. Does the patient have an abnormality in an iron overload screening test, a family history of iron overload or hemochromatosis, or histological iron of greater than 3+:



15. Date of blood draw for HFE gene analysis:

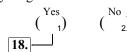
=		_
day	mon	year

16. Type of abnormality (WT = wild type; check only one):

None	(0)
C282Y/H63D heterozygote mutation	(1)
C282Y/C282Y homozygote mutation	(2)
C282Y/WT heterozygote mutation	(3)
H63D/WT heterozygote mutation	(4)
H63D/H63D homozygote mutation	(5)

E. Ceruloplasmin

17. Is patient 40 years old or younger:



a. Is a ceruloplasmin value available:

18. Date of blood draw for ceruloplasmin: (required only if patient is 40 years old or younger; record if available if patient is greater than 40 years old):



Repeat if date is greater than 10 years prior to screening.

- 19. Ceruloplasmin ____ _ __ __ __
 - a. Upper limit of normal: ______ mg/dL
 - **b.** Lower limit of normal: _____ mg/dL ____

F.	Alpha-1	l antitr	vpsin

20. Date of blood draw for alpha-1 antitrypsin (A1AT):

day mon year

Repeat if date is greater than 10 years prior to screening.

a. Upper limit of normal: _____ mg/dL ____

- **b.** Lower limit of normal: $\underline{\qquad}_{mg/dL}$
- **22.** A1AT phenotype:

a. Pi Z heterozygote:

Yes (1)
No (2)
Unknown (3)

b. Pi ZZ homozygote: Yes (

No (2)
Unknown (2)

23. A1AT deficiency (physician judgment):



G. Autoantibody studies

24. Date of blood draw for autoantibody tests:

day mon year

Repeat if date is greater than 5 years prior to screening.

25. Antinuclear antibody (ANA):

Positive (*1)
Negative (26.

- *If positive ANA value, complete either a or b depending on laboratory results:
- **a.** Titer (record only the denominator):

1/ ____ ___

b. Units: ____ _ _ _

26. Antismooth muscle antibody (ASMA):

Positive (*₁)
Negative (₂)

*If positive ASMA value, complete either a or b depending on laboratory results:

a. Titer (record only the denominator):

1/____ ____

- 27. Antimitochondrial antibody (AMA):

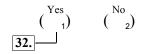
Positive $(*_1)$ Negative (28.Age < 18 and not done (3)

*If positive AMA value, complete either a or b depending on laboratory results:

a. Titer (record only the denominator):

1/____ ____

- **28.** Is patient 18 or older:



29. Lymphocytotoxic antibody (LCA):

Positive

Negative

Not available

(*1)

30.

30.

30.

30.

*If positive LCA value, complete either a or b depending on laboratory results:

a. Titer (record only the denominator):

1/_____

30. Antibody to liver-kidney microsomal antigen (LKM1):



*If positive LKM1 value, complete either a or b depending on laboratory results:

a. Titer (record only the denominator):

1/		

- **b.** Units:
- **31.** Rheumatoid factor (RF):

Positive	(*1
Negative	(2
Not available	32.
*If positive record RF value	32.

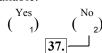
If positive, record RF value.

a. Units:	<u> </u>
	IU/mL

If results are given as a titer, record as "n" and key the actual result in the General Comments.

H. Immunoglobulin levels

32. Are immunoglobulin levels available:



33. Date of blood draw for immunoglobulin levels:

		_
day	mon	year

- **34.** IgA: mg/dL
- **35.** IgG: mg/dL
- **36.** IgM: mg/dL

I. Other screening blood tests

37. Date of blood draw for thyroid stimulating hormone (TSH)*:

=		_
day	mon	year

Repeat if date is greater than 5 years prior to screening. *Optional if patient under age 18; enter "m" if not done.

38. Thyroid stimulating hormone:

•	
 μU/mL	

- J. Administrative information
- **39.** Study Physician PIN:
- **40.** Study Physician signature:
- 41. Clinical Coordinator PIN:
- **42.** Clinical Coordinator signature:
- **43.** Date form reviewed:

_		_
day	mon	year

LT - Liver Tissue Banking

Purpose: To document collection of extra liver tissue and procedures for liver tissue banking.

When: Whenever more than 2 cm of liver tissue are obtained during a biopsy. Use visit code to, to48, to96, t144. t192, t240, t288, t336, t384, t432, or t480 (check the patient's visit time window guide for the visit that is currently open). If the biopsy is after

enrollment and before the t048 window is open, use visit code n. This form is expected when the Liver Biopsy Materials Documentation (SD) form says liver tissue was obtained for banking.

By whom: Clinical Coordinator, in consultation with study physician.

Instructions: Liver biopsy tissue should be obtained by a needle core biopsy (as opposed to a wedge biopsy) using a 16 gauge or greater needle. Whenever more than 2 cm of tissue are obtained during biopsy, place a 1-2 mm segment of liver tissue into a labeled 2.0 mL polypropylene cryovial pre-filled with approximately 1 mL of RNAlater® Solution. Liver tissue should be placed in RNAlater® Solution within one minute and no more than 5 minutes after biopsy. Note: If the sample is not placed in RNAlater® Solution within 5 minutes, discard the cryovial. Refrigerate the cryovial at 4° C overnight to allow thorough penetration of the liver tissue and then transfer to -70° C freezer for storage. Batch ship cryovials monthly on dry ice to the NIDDK Biosample Repository located at Fisher BioServices.

A. Center, patient and vis	it identificatio	n	11. Was liver tissue refrigerated at 4° C overnight, then transferred to freezer for
1. Center ID:			storage: Yes No
2. Patient ID:			$ \begin{array}{ccc} & & & \\ & & \\ \hline &$
3. Patient code:			a. If no, describe conditions of local storage:
4. Date form initiated:			
	mon	year	
5. Visit code:			C. Cryovial label
6. Form & revision:		_t2_	12. Attach duplicate cryovial label (make sure you attach the duplicate of the label attached to the cryovial holding the liver tissue from this biopsy):
7. Study: NA	AFLD Databa	se 2 <u>6</u>	
B. Liver biopsy/RNA <i>later</i> procedures	® Solution sto	rage	
8. Date of biopsy:			
day	mon	year	
9. Was the liver tissue obneedle core biopsy (as biopsy):	s opposed to a	0	D. Administrative information
	$\binom{\text{Yes}}{1}$) (No ₂)	13. Clinical Coordinator PIN:
10. Was liver tissue placed Solution preferably wi no more than 5 minute	thin 1 minute,		14. Clinical Coordinator signature:
	Yes () (^{No} ₂)	15. Date form reviewed:
* Discard liver tissue			day mon year

NAFLD Database 2

MV - Missed or Incomplete Visit

Purpose: Record reason(s) for missed or incomplete visit.

When: At the close of a visit window for any missed followup visit or for any followup visit with specific forms not completed. Use visit code t048, t096, t144, t192, t240, t288, t336, t384, t432, or t480.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in

missing forms) within the time window for the visit.

A. Center, patient, and visit identification	10. Steps taken to avoid missing the visit (check all that apply)
1. Center ID:	a. Telephoned patient: (
	b. Mailed reminder card: (
2. Patient ID:	c. Other (specify):
3. Patient code:	specify
4. Date of visit:	14.
day mon year	D. Missed form information
5. Visit code:t	11. Check form(s) not completed (check required forms that were missed)
6. Form & revision:mv1_	a. Blood Processing for Plasma and Serum (BP): (
7. Study: NAFLD Database 2 6	b. Followup Medical History (HI): (
B. Reason for completion of this form	c. Laboratory Results - Tests Done During Screening and Followup (LR): (
-	d. Physical Examination (PE): (
8. Was the entire visit missed: Yes No	e. Other (specify): (
	specify
C. Missed visit information	12. Reason form(s) not completed (check all that apply)
9. Reason for missed visit (check all that apply)	a. Patient was ill:
a. Patient was ill:	b. Patient refused procedure: (
b. Patient was temporarily away from	c. Parent refused procedure: (
area: (1) c. Patient refused to return: (1)	d. Procedure forgotten:
c. Patient refused to return: (1)d. Patient has permanently moved from	e. Other (specify):
the area:	
e. Unable to contact patient:	specify
f. Other (specify):	

specify

Patient ID:		

13. Attempts made to complete form(s) <i>(check apply)</i>	allı	hat
a. Attempted to reschedule procedure:	(1)
b. Attempted to collect interview data by phone from patient/family:	(1)
c. Attempted to gain patient/parent cooperation:	(1)
d. Other (specify):	(1)
specify		
E. Administrative information		
14. Clinical Coordinator PIN:		
15. Clinical Coordinator signature:		
16. Date form reviewed:		
day mon	year	

NAFLD Database 2

PE - Physical Examination

Purpose: Record physical exam findings of NAFLD Database 2 patients. When: Visits t0, t048, t096, t144, t192, t240, t288, t336, t384, t432, and t480.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurement are found in the NAFLD Database 2 SOP I. In brief: height, weight, waist and hips should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 inches (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 inches (10.2 cm) of each other.

A. Center, patient, and visit identification		9. Weight (shoes off - repeat wer until you have two measurement kg) of each other):	
1. Center ID:		a. 1st measurement:	
2 P. C. A.D.		a. 1st measurement.	•
2. Patient ID:			- — — —
		b. 2nd measurement:	
3. Patient code:			· •
A THE STATE OF THE		c. Units:	
4. Visit date:		Pounds	(1)
day mon	vear	Kilograms	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
day illoli	year	10 Weigh (adam din a memi da ainel a	41.:-14:4
5. Visit code:t		10. Waist (standing, at midpoint bet of iliac crest and lowest point repeat waist measurements u measurements within 4 in (10.2	of costal margin; ntil you have two
6. Form & revision:p	e1_	a. 1st measurement:	em) of each other)
		a. 1st measurement.	
7. Study: NAFLD Database	2 6		· —— — —
		b. 2nd measurement:	
B. Measurements			•
		c. Units:	
8. Height (shoes off - repeat height measurtily you have two measurements within	surements	Inches	(1)
(1.3 cm) of each other):	0.5 inches	Centimeters	$\begin{pmatrix} & & & & & & & \\ & & & & & & & \\ & & & & & & & \end{pmatrix}$
a. 1st measurement:			. 2
b. 2nd measurement:	<u>•</u>	11. Hip (standing, at fullest part of a measurements until you have within 4 inches (10.2 cm) of ea	two measurements
b. 2nd measurement.		a. 1st measurement:	
	<u> </u>		•
c. Units:		b. 2nd measurement:	
Inches	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	b. 2nd measurement.	
Centimeters	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$		·
		c. Units:	
		Inches	(1)
		Centimeters	(2)

12.	Temperature (oral or other as age):	appropriate	for	D. Liver signs		
	0 /			18. Focused liver signs (check all that apply)		
	a. Degrees:			a. None:	(1)
	b. Scale:			b. Jaundice:	(1)
	Fahrenheit:	(1)	c. Palmar erythema:	(1)
	Centigrade:	(2)	d. Contractures:	(1)
13.	Blood pressure			e. Pedal edema:	(1)
	1			f. Spider angiomata:	(1)
	a. Systolic:	mmHg		g. Asterixis:	(1)
		8		h. Hepatic encephalopathy:	(1)
	b. Diastolic:			i. Other, (specify):	(1)
		mmig				17
14.	Resting radial pulse:	beats/minute	_	specify		
15.	Respiratory rate:	breaths/mi	 nute	E. Tanner Staging		
C. E	xamination findings			19. Is Tanner staging required for this patient (Note: Required during screening if patient is 17 years old or younger.) (che		onlv
16.	Areas with acanthosis nigricans (check all that apply):			one):	ch c	····y
	a. None:	(1)	Yes, patient has not reached full sexual maturity and is 17 years old or younger:	()
	b. Neck:	(1)	No, patient is 18 years old or older	(₁) ₂)
	c. Axilla:	(1)	27	7.]—	
	d. Elbows:	(No, participant had reached full sexual		
	e. Knees:	(1)	maturity (Tanner stage 5 on all parameters at screening or for 2		
		(1)	consecutive visits)	_ (3)
	f. Knuckles:	(1)	27	7.	_ا
	g. Periumbilical:	(1)	20. Is the patient female:		
17.	Abdomen abnormalities present			$\binom{\mathrm{Yes}}{1}$	(No
	(check all that apply): a. None:	()	23.		
	b. Ascites:	(1)			
		(1)	Male Tanner Staging		
	c. Obese:	(1)	21. Genital stage:		
	d. Splenomegaly:	(1)	21. John Suge.		1-5
	e. Hepatomegaly:	(1)	22. Pubic hair stage:		
	If Yes, span at right midclavici	ılar line:		40.0 5		1-5
				23	7.	╛

Female Tanner Staging

- 23. Breast stage:
- **24.** Pubic hair stage:
- **25.** Has menarche occurred:

1-5

26. If yes, what was the patient's age at menarche:

age in years

F. Administrative information

28. Study Physician signature:

- **27.** Study Physician PIN: ____ ___
- **29.** Clinical Coordinator PIN:
- **30.** Clinical Coordinator signature:
- ____
- **31.** Date form reviewed:

_		_	
day	mon		year

NAFLD Database 2

RC - Rescreen in Database 2

Purpose: To rescreen a patient who was previously found to be ineligible for the NAFLD Database due to a temporary ineligibility. This form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 90-day screening window is reckoned from). The original RG form completed for the patient must remain in the data system. New screening phase tube and questionnaire labels will be available for printing upon keying this form.

When: Visit code t0.

Administered by: Clinical Coordinator.

Respondent: None.

Instructions: Complete this form for a patient who was previously found to be ineligible for the NAFLD Database due to a temporary ineligibility and who now wants to rescreen for the NAFLD Database 2. In general, the patient must complete all Database 2 screening data collection anew and all previously keyed Database 2 screening forms should be deleted from the data system except the RG and possibly the CG forms. Update sections B, C, and F of the RG form and update the keyed record (you cannot delete the RG form). If blood was collected successfully for the Genetics Repository, a new sample does not need to be collected and the previously completed CG form may remain unchanged in the data system.

A. Center, patient, and	visit identification	C. Administrative inform	mation	
1. Center ID:		9. Clinical Coordinator	PIN:	
2. Patient ID:		10. Clinical Coordinator	signature:	
3. Patient code:		11. Date form reviewed:		
4. Date of visit:	_		mon	year
day	mon year			
5. Visit code:	_t0			
6. Form & revision:	<u>r_c_1</u>			
7. Study:	NAFLD Database 2 6			
B. NAFLD Database pa	articipation			
8. Date in item 4 of or form:	iginal Database RG			
day	mon year			

RG - Registration

Purpose: To register patients as candidates for enrollment in the NAFLD Database 2 study and to assign a patient ID number. This is the first form completed for a NAFLD Database 2 patient. The Registration Form must be the first form keyed, before any other NAFLD Database 2 forms.

When: At first screening visit (t0). Administered by: Clinical Coordinator.

Respondent: Patient and parent (if patient is age 17 or younger).

Instructions: Use Flash Cards as instructed. Do not assign an ID if patient has previously been assigned an ID for a NASH CRN study.

TWISH CITY Study.			
A. Center, patient and vis	sit identification	12. Ethnic category (show the patient/park Card #1 and ask the respondent to pick gory that describes the patient best; c	the cate-
1. Center 1D.		one):	
2. Patient ID:		Hispanic or Latino or Latina	(1)
_, _ , _ , _ ,		Not Hispanic, not Latino, not Latina	(
3. Patient code:		<u> </u>	14.
4. Visit date: day		13. What describes your Hispanic, Latino, or Latina origin best (show the patient/par Card #1 and ask the respondent to pick category that best describes their Hisp ino, or Latina origin; check only one):	ent Flash k the sub-
5. Visit code:	t 0	Mexican	(1)
5. Visit code.	<u> </u>	Puerto Rican	(2)
6. Form & revision:	<u>r g 1</u>	Cuban	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
00 1 01111 00 10 1101011		South or Central American	(4)
7. Study: NA	AFLD Database 2 <u>6</u>	Other Spanish culture or origin	(5)
B. Consent		specify	
8. Has the patient (or pat signed the NAFLD Da consent statement:	atabase 2 informed	14. Racial category (show the patient/park Card #2 and ask the respondent to pick gory or categories that describe the pac check all that apply)	the cate-
	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	a. American Indian or Alaska Native:	(1)
	STOP]—	b. Asian:	(1)
C. Information about pat	ient	c. Black, African American, Negro, or Haitian:	(1)
9. Date of birth:		d. Native Hawaiian or other Pacific Islander:	(1)
day month		e. White:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
Record 4-digit year f	or date of birth.	f. Patient refused:	(1)
10. Age at last birthday:	years	15. In what country was the patient born <i>(coone):</i>	heck only
11. Gender:		Continental US (includes Alaska) or Hawaii	()
Male	()	Other, (specify):	(1)
Female	$\begin{pmatrix} & & & & & & & & & & \\ & & & & & & & & $	omer, (specify).	(₂)
1 ciliaic	(2)	specify	
		1 2	

16. Highest educational level achieved by patient (show the patient/parent Flash (ask the respondent to pick the categors scribes the patient best; check only one Never attended school	ory that		22. Combined annual income before taxes all members of patient's household (show the patient/parent Flash Card the respondent to pick the category that the patient's combined household incoheck only one):	#6 and ask t describes
Kindergarten, pre kindergarten, or	(`	Less than \$15,000	(1)
younger	(1)	\$15,000 - \$29,999	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$
Grades 1 to 5	(2)	\$30,000 - \$49,999	$\begin{pmatrix} 2 \\ 3 \end{pmatrix}$
Grades 6-8	(3)	\$50,000 or more	(3)
Grades 9-11	(4)	\$20,000 of more	(4)
Completed high school	(₅)	D. Previous registration in a NASH CRN	study
Some college or post high school education or training	(6)	23. Has the patient ever been assigned an I	D
Bachelor's degree or higher 17. Is the patient currently employed: Yes	(7) No (number in a NASH CRN study: (Yes (1)	(No 2)
(₁) 18. What is the patient's current occupation	(20.—	₂)	24. In which NASH CRN studies has the patient previously been registered (che apply)a. Database:	ck all that $\begin{pmatrix} 1 \end{pmatrix}$
specify occupation			b. PIVENS:	(1)
19. About how many hours does the patier	nt		c. TONIC:	(1)
work each week:	# hour	s	d. Other, (specify):	(1)
20. Which of the following categories best	+		specify	
characterizes the patient's occupationa history (show the patient/parent Flash (ask the respondent to pick the catego scribes the patient best; check only on	l Card #4 ory that		25. ID Number previously assigned to patient <i>ID in item 2):</i>	ent (record
Never employed	(0	26 6 1	1
Laborer	(1)	26. Code previously assigned to patient (retient code in item 3):	ecord pa-
Clerical	(2)	,	
Professional	(3)		
Homemaker	(4)		28.
Other, (specify):	Ì	5)	E ID aggious and	
, (1 32)		3/	F. ID assignment (If a STOP condition was checked in sec	ction R the
specify			patient is ineligible and a Patient ID sh assigned. If the patient was previously in a NASH CRN study, a new ID num	ould not be registered
21. Marital status of the patient (show the patient/parent Flash Card the respondent to pick the category the the patient best; check only one):			not be assigned.)27. Place ID label below and record Patien ID in item 2 and patient code in item 3.	
Single, never married	(1)		
Married or living in marriage-like	,	,	CCCC ####	
relationship	(2)	CCCC ####, zzz	
Separated, divorced, or annulled	(3)		
Widowed	(4)		

Patient ID:	 	

\mathbf{C}	۱dm	inict	•ative	info	rmation

28. Clinical Coordinator PIN:

29. Clinical Coordinator signature:

30. Date form reviewed:

mon year

NAFLD Database 2

SD - Liver Biopsy Materials Documentation

Purpose: To document whether liver tissue was obtained for banking and whether the biopsy is adequate for scoring; if adequate for scoring, the number and type of slides available for archival at the DCC are noted. If slides cannot be archived at the DCC, the source of the slides and the date by which the slides that must be returned to the clinical center are recorded.

When: As needed during screening (visit t0) and follow-up (visits t048, t096, t144, t192, t240, t288, t336, t384, t432, or t480). During follow-up, specify the code for the follow-up visit that is currently open (check the patient's visit time window guide). If no window is open (i.e., right after enrollment) use visit code "n".

By whom: Clinical Coordinator.

Instructions: This form is used to document acquisition of tissue and slides from liver biopsies. The SD form provides information about the tissue and slides from the reported liver biopsy and alerts the DCC to expect completion of the Liver Tissue Banking (LT) form, receipt of tissue at the Biosample Repository, and receipt of slides from the biopsy at the DCC. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. If fewer than 2 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 2 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC.

A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and ID code (use labels provided - PRpt), and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of liver biopsy. The liver biopsy slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60; the borrowed slides should be labeled on the back of the slide with removable labels with sequence numbers 81-90.

1. Center code:

2. Patient ID:				
3. Patient code:				
4. Date form initia	ted:			
day	mon			/ear
5. Visit code (t0 o currently open)		ow-up	visit	that is
6. Form & revision	1:	_S_	<u>d</u>	_1_
7. Study:	NAFLD D	ataba	se 2	6

B. Surgical pathology report

8.	Was a copy of the surgical pathology		
	report for the liver biopsy obtained:		
	Yes) (*	0
	$(+_1)$) (.	2)
		26.	J

- + Annotate the report with the patient's NASH CRN ID number and code (you may use one of the pathology labels), black out the patient's name, and attach the report to this form.
- * This biopsy cannot be used for the NAFLD Database 2 study.
- **9.** Biopsy information
 - a. Date of liver biopsy specified on the surgical pathology report:

_		_
day	mon	veer
uay	111011	ycai

b. Lobe specimen obtained from (check only one):

C. Biopsy specimens and stained slides at the clinical center

10. Was a sample of liver tissue obtained for banking:

* If Yes, complete the Liver Tissue Banking (LT) form

- 11. Is this visit t0 (ie, a patient currently in screening):

 Yes

 11.
- **12.** Were you able to obtain stained slides from this biopsy for local evaluation and were they adequate for scoring:

Yes $\begin{pmatrix} Yes \\ + \\ 1 \end{pmatrix}$ $\begin{pmatrix} No \\ * \\ 26. \end{pmatrix}$

- + Continue with this form and also complete form HF.
- * This biopsy cannot be used for the NAFLD Database 2.
- **13.** What stained slides from the biopsy are available for local evaluation *(check all that apply)*

a. H & E stain: (1)

b. Masson's trichrome stain: (1)

D. Unstained slides to be sent to the DCC

14. Are unstained slides available for sending to the DCC:



15. How many unstained slides will be sent to the DCC:

16. What are the slide sequence numbers for those slides *(from the NASH CRN labels on each slide - use permanent labels, sequence numbers 01-60)*

a. Slide sequence number:

01-60

b. Slide sequence number:

01-60

d. Slide sequence number:

c. Slide sequence number:

01-60

e. Slide sequence number:

01-60

f. Slide sequence number:

01-60

g. Slide sequence number:

01-60

h. Slide sequence number:

i. Slide sequence number:

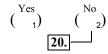
01-60

j. Slide sequence number:

01-60

E. Stained slides to be sent to the DCC

17. Is the institution's H & E stained slide to be sent to the DCC:



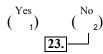
18. Slide sequence number for this slide (from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):

81-90

19. Is the H & E stained slide to be returned to the clinical center:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

20. Is the institution's Masson's trichrome stained slide to be sent to the DCC:



21. Slide sequence number for slide (from the NASH CRN label on the slide - use removable labels, sequence numbers 81-90):

81-90

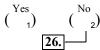
NAFLD Database 2

Patient ID:		

22. Is the Masson's trichrome slide to be returned to the clinical center:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

23. Is at least one of the stained slides to be returned to the clinical center (i.e., either item 19 = yes or item 22 = yes):



24. When do the stained slides need to be returned to the clinical center *(check only one)*:

Immediately after central review (1)

At the end of the NASH CRN funding period

(2)

25. Which pathology department did these slides come from *(check only one):*

NASH CRN clinical center's pathology department

Other, (specify):

26. (₂)

name

address

address

address

phone

Note: This is the Database 2 record of the source of the slides, i.e., where the clinical center should send the slides when they are received back from the DCC.

F. Administrative information

26. Clinical Coordinator PIN:

27. Clinical Coordinator signature:

28. Date form reviewed:

day mon year

CONFIDENTIAL: Not for Citation or Distribution

Transfer Notification

Purpose: To record a transfer from one center to another center.

When: Upon transferring from the current center and prior to the first visit at the adopting center.

By whom: Clinical coordinator of each center (current center: sections A-C, adopting center: sections D- E).

Instruction: For current center: When patient notifies current center of upcoming transfer, the current clinical coordinator should (1) complete Sections A-C of the Transfer Notification (TN Form), (2) send the TN form to the adopting center, with a copy of the most recent completed HI, LR, and PE forms, (3) send the labels for cryovials and slides and a copy of the visit window schedule to the adopting center. For adopting center: Prior to the patient coming to the adopting center, the adopting clinical coordinator should: (1) complete Sections D-E of the TN form, (2) Fax the TN form to the DCC (Fax: 410-955-0932). The DCC will key the form.

A. Current center and pation	ent identification	13. Clinical coordinator signature:
1. Center ID:		
2. Patient ID:		D. Adopting center, patient and visit identification 14. Adopting center ID:
3. Patient code:		
4. Date of notification of it	ntent to transfer:	15. Patient ID (must be same as in Section A):
	mon year	16. Patient code (must be same as in Section A):
5. Visit code:	_n	
6. Form & revision:	<u>t</u> n 1	17. Expected date of first followup visit at adopting center:
7. Study: NA	FLD Database 2 <u>6</u>	day mon year
B. Last followup visit infor	mation	18. Visit ID code for expected first followup visit at adopting center:
8. Date of last followup vi	sit:	
	mon year	Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.
9. Visit ID code of last corvisit:	mpleted followup	E. Adopting center administrative information
		19. Date form reviewed:
10. Have cryovial and slide	labels been sent	day mon year
to the adopting center:	$ \begin{pmatrix} Yes & No \\ \begin{pmatrix} 1 \end{pmatrix} & \begin{pmatrix} *_2 \end{pmatrix} $	20. Clinical coordinator PIN:
* Send the cryovial and slide lab		21. Clinical coordinator signature:
C. Current center administ	rative information	
11. Date form reviewed:	_	Fax form to the DCC. The DCC will key the TN form.
day	mon year	•

12. Clinical coordinator PIN:

NASH CRN FLINT

FLINT Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
BG	Baseline History
BP	Blood Processing for Plasma and Serum
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
CV	Cardiovascular Risk Factors
DR	Death Report
HF	Liver Biopsy Histology Findings
HI	Follow-up Medical History
ΙE	Interim Event Report
LD	Lifetime Drinking History (Skinner)
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LT	Liver Tissue Banking
MR	MRI Report
MV	Missed or Incomplete Visit
PE	Physical Examination
PF	Focused Physical Examination
QF	MOS 36-Item Short-Form Health Survey
RC	Rescreen Form
RD	Study Drug Dispensing and Return
RG	Registration
RZ	Randomization Checks
SD	Liver Biopsy Materials Documentation
SR	Serious Adverse Event/IND Safety Report
TN	Transfer Notification

FLINT

AD – Alcohol Use Disorders Identification Test (AUDIT)

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.

When: Screening visit s.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and review completed forms.

Respondent: Patient.

Instructions: Flash Card #9, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator then should complete section B below.

A. Co	enter, patient, and vi	sit identificati	ion		<mark>lministrative information</mark> To be completed by Clinical Coordinator a	fter	
1.	Center ID:			SI	urvey is completed.)		
2.	Patient ID:			8.	How was the questionnaire completed:		
3.	Patient code:				Self-administered by patient Interview with translator	(1) 2)
4.	Date of visit (date p	atient complet	ted the form):			`	2/
		mon	year	9.	Clinical Coordinator a. PIN: b. Signature:		
5.	Visit code:				z. signwart.		
6.	Form & revision:	<u>a</u>	d1_	10.	Date form reviewed:		
7.	Study:		FLINT 7				
					day mon	vear	

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below (*items 1-10 are for clinical center use only*).

11. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times a month	Two to three times a week	Four or more times a week
	(1)	(2)	(3)	(4)

12. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more
(0	(1)	(₂)	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

13. How often do you have six or more drinks on one occasion?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
()	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	(4)

14. How often during the last year have you found that you were not able to stop drinking once you had started?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$

15. How often during the last year have you failed to do what was normally expected from you because of drinking?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

Patient ID:		

16.	How often during the last year have you needed a first drink in the morning to get yourself going
	after a heavy drinking session?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 4 \end{pmatrix}$

17. How often during the last year have you had a feeling of guilt or remorse after drinking?

	Less than			Daily or	
Never	monthly	Monthly	Weekly	almost daily	
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)	

18. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

	Less than	Daily or		
Never	monthly	Monthly	Weekly	almost daily
(0)	$\begin{pmatrix} & & 1 \end{pmatrix}$	(2)	$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$	(4)

19. Have you or someone else been injured as a result of your drinking?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

20. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & & \\ & & & \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

21. Today's date:

Thank you for completing this questionnaire.

FLINT

BG - Baseline History

Purpose: To collect baseline history information about the patient.

When: Visit s.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview and chart review. If c is checked for an item, and the physician agrees with the diagnosis, the patient is ineligible for the FLINT Trial. If is checked for an item, the patient is ineligible and cannot enroll in the FLINT Trial; the form should not be keyed to the data system; but the form should be set aside with forms for other patients who started screening, but were found to be ineligible.

•	C 4					4.0.	4
Α.	Center.	VISIT.	ana	patient	ıaen	unca	tion

- **2.** Patient ID: ____ ___ ____
- **3.** Patient code: ____ ___
- **4.** Visit date (date this form is initiated):

_		_
day	mon	year

- 5. Visit code: S
- **6.** Form & revision: <u>b g 2</u>
- 7. Study: FLINT 7

B. NAFLD history

8. Does the patient have a liver biopsy done that you want evaluated for the FLINT trial (complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy):



*Randomization must be done within 90 days of liver biopsy.

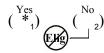
9. Date of liver biopsy:

=		=
day	mon	year

10. Last day to randomize based on liver biopsy date (90 days after biopsy; use date calculator 2 on the NASH CRN home page):



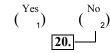
11. Will the patient have a biopsy during screening:



*Complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy. Blood draw for banking should be done **prior** to the biopsy or at least 4 days **after** the biopsy.

C. Menstrual history and use of effective birth control

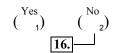
12. Is the patient female:



13. Characterize the menstrual history in the past 5 years (*check only one*):

Regular periods	(1)
Irregular periods	(2)
Rare periods	(3)
No periods	(4)

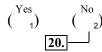
14. Is patient post-menopausal:



15. What was the patient's age at menopause:

	_	
	<u> </u>	
age	ın	years

16. Is the patient female and of childbearing potential:



17. Is the patient currently pregnant:

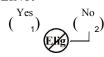


18. Is the patient currently breast feeding:



*Caution: Patient cannot be breastfeeding at time of randomization.

19. Is the patient willing to use effective birth control methods during FLINT:



- **D. Medical history** (means Caution; condition is exclusionary if study physician agrees with diagnosis; means the patient is ineligible and can not enroll in FLINT)
- **20.** Has the patient ever been diagnosed with any of the following (check all that apply; source of information can be interview and/or chart review)
 - a. Diabetes type 1:
 - **b.** Diabetes type 2:
 - c. Chronic hepatitis B:



d. Hepatitis C:



e. Active autoimmune hepatitis:



- **f.** Autoimmune cholestatic liver disorder (PBC):
 - (TBC).
- g. Wilson's disease:
- h. Alpha-1-antitrypsin (A1AT) deficiency:
- i. Glycogen storage disease:
- j. Iron overload:
- k. Hemochromatosis:
- 1. Polycystic liver disease:
- m. Biliary diversion:
- n. Primary sclerosing cholangitis:
- o. Drug induced liver disease:
- p. Bile duct obstruction:
- **q.** Gilbert's syndrome: (1)
- r. Esophageal or gastric varices on endoscopy:
- s. Bleeding from varices:
- t. Other gastrointestinal bleeding:
- u. Ascites:
- v. Edema:
- w. Hepatic encephalopathy:
- x. Portal hypertension:

y. Hepatorenal syndrome:		1)	ba. Major depression: (1)
	(Fug)—		bb. Schizophrenia: (1)
z. Hepatopulmonary syndrome:		1)	bc. Bipolar disorder: (1)
	(Fug)—		bd. Obsessive compulsive disorder: (1)
aa. Short bowel syndrome:	<u>(</u>	1)	be. Severe anxiety or personality disorder: (1)
ab. Hemophilia (bleeding disorder):	<u>(</u>	1)	bf. Substance abuse:
ac. HIV positive:		1)	bg. Other (specify):
ad. Systemic autoimmune disorder su	ıch		specify
as rheumatoid arthritis or systemi lupus:	,	1)	bh. None of the above: $\begin{pmatrix} 1 \end{pmatrix}$
ae. Endocrine disease (hormonal abnormality):	(21.	. Has the patient ever had surgery for any of the following (check all that apply)
af. Hepatocellular carcinoma:		1)	a. Stapling or banding of the stomach: (1)
ag. Other malignancy (cancer):	(,	1)	b. Jejunoileal (or other intestinal) bypass
ah. Peripheral neuropathy:	(,	1)	prior to the diagnosis of NAFLD:
ai. Seizure disorder or epilepsy:	(,	1)	ichig)—
aj. Drug allergies:	(,	1)	c. Biliopancreatic diversion:
ak. Hypothyroidism:	(,	1)	Other CL or horistric surroum (sussifil)
al. Hypertension:	(,	1)	d. Other GI or bariatric surgery (specify):
am. Cerebrovascular disease:	(,	1)	<u>/C\</u>
an. Chronic cholestasis:	(,	1)	specify
ao. Hyperlipidemia (high cholesterol, high triglycerides):		1)	e. None of the above: (1)
ap. Pancreatitis:	(,	₁) _{22.}	. Is the patient currently undergoing
aq. Cholelithiasis:	(,	1)	evaluation for bariatric surgery:
ar. Coronary artery disease:	(,	1)	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
as. Congestive heart failure:	(,	1)	<u></u>
at. Elevated uric acid such as gout:	(,	1)	Organ, limb, or bone marrow transplant
au. Kidney disease:	(,	1)	a. Has the patient ever received a liver
av. Polycystic ovary syndrome:	(,	1)	transplant:
aw. Sleep apnea (not breathing during sleep):	(,	1)	$\left(\begin{array}{c} \operatorname{Yes} \\ 1 \end{array}\right)$ [Fig. 1]
ax. Dermatologic disorders:	(,	1)	
ay. Myopathy:	(,	1)	b. Has the patient ever received any other organ, limb, or bone marrow
az. Myositis:	(,	1)	transplant:
			$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

E. Drugs historically associated with NAFLD

24.	Has the patient used any of the following
	in the past year (check all that apply)

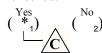
a.	Amiodarone	(Pacerone):	1)	

ı.	Other known hepatotoxin #2 (specify):	(.)

	Othor	1	1	12	(:£.).	7	
m	. Otner	known	hepatotoxin #	Ŧ3	(specify):	(1 <i>)</i>

n. None of the above: (1)

25. Were any of the items on 24a-m checked:

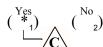


*Caution: Use of any of these drugs for more than 2 weeks in the past year is exclusionary.

26.	Has the patient taken any systemic
	glucocorticoids in the past year
	(check all that apply):

a. Betamethasone sodium (Celestone):	(1)

27. Were any of the items 26a-k checked:



*Caution: Use of systemic glucocorticoids for more than 2 weeks in the past year is exclusionary.

28.	Has the patient taken any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective			x. Other, (specify):	(1)
	estrogen receptor modulators in the past year (check all that apply):			y. Other, (specify):	(1)
	a. Boldenone undecylenate (Equipoise):	(1)			
	b. Conjugated estrogen (Premarin/Prempro):	(1)	z. None of the above:29. Were any of the items 28a-y checked:	(1)
	c. Diethylstilbestrol and methyltestosterone (Tylosterone):	(1)	Yes (*)	(^N	No 2)
	d. Esterified estrogen (Estratab, Menest):	(1)		7	
	e. Estradiol (Estrace):	(1)	*Caution: Use of anabolic steroids, tamox, estrogens at doses greater than those us		
	f. Ethinyl estradiol (Estinyl):	(1)	hormone replacement for more than 2 week	s in	the
	g. Fluoxymesterone (Android-F,		.,	past year is exclusionary.		
	Halotestin):	(1)	F. Use of antiNASH drugs and supplements		
	h. Levonorgestrel (Norplant):	(1)	20. Has the notion tolers any of these		
	i. Medroxyprogesterone (Cycrin, Provera):	(1)	30. Has the patient taken any of these antiNASH drugs in the past 6 months: Yes	1	No .
	j. Megestrol (Megace):	(1)	(1)	(2)
	k. Methandrostenolone (Dianabol):	(1)	(If yes, check all that apply):]	J
	l. Methyltestosterone (Android):	(1)	a. Betaine (Cystadone):	(1)
	 m. Nandrolone (Deca-Durabolin, Durabolin, Hybolin Decanoate, Kabolin): 	(,	b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler):	(1)
	,	(1)	c. Ursodeoxycholic acid (UDCA,		
	n. Norethindrone (Micronor):	(1)	Actigall, URSO, Ursodiol):	(1)
	o. Norgestrel (Ovrette):	(1)	d. S-adenylmethionine (SAM-e):	(1)
	p. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon,			e. Milk thistle:	(1)
	Levlen, Levlite, Levora, Loestrin,			f. Probiotics (any form):	(1)
	Lo-Ovral, Necon, Nelova, Nordette, Norethin, Norinyl, Ortho Cyclen, Ortho-Novum, Ortho Tri-Cyclen,			g. Other (specify):	(1)
	Ovral, Tri-Levlen, Triphasil, Trivora, Zovia):	(1)	specify		
	q. Oxandrolone (Oxandrin):	(1)	31. Has the patient taken a thiazolidinedione		
	r. Oxymetholone (Anadrol):	(1)	in the past 6 months:		
	s. Progesterone (Prometrium):	(1)	$\begin{pmatrix} \text{Yes} \\ \begin{pmatrix} 1 \end{pmatrix} \end{pmatrix}$	(No 2)
	t. Raloxifene (Evista):	(1)			
	u. Stanzolol (Winstrol):	(,)			
	v. Tamoxifen (Nolvadex):	(1)			
	w. Testosterone (Depo-Testosterone):	(1)			
		١.	1/			

G. Use of antiobesity drugs

32. Has the patient taken any antiobesity medications in the past 6 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	33.

1)

(If yes, check all that apply):

- **a.** Dexfenfluramine hydrochloride (Redux): (1)
- **b.** Fenfluramine hydrochloride (Pondimin):
- c. Methamphetamine hydrochloride (Desoxyn, Gradumet):
- **d.** Orlistat (Xenical):
- e. Phendimetrazine tartrate (Adipost, Bontril):
- **f.** Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
- **g.** Sibutramine hydrochloride monohydrate (Meridia):
- **h.** Other, (specify):
- i. Other, (specify):

H. Use of antidependency drugs

- **33.** Has the patient taken any alcohol abuse, inhaled or injection drugs (dependence or withdrawal) medications in the past 12 months (check all that apply):
 - **a.** Chlordiazepoxide (Librium): (1)
 - **b.** Clorazepate dipotassium (Tranxene): (1)
 - c. Diazepam (Valium):
 - **d.** Disulfiram (Antabuse):
 - e. Hydroxyzine pamoate (Vistaril):
 - **f.** Naltrexone hydrochloride (Revia): (1)
 - g. Other, (specify):
 - h. None of the above:

34. Were any of the items 33a-g checked:



*Caution: Active substance abuse, such as alcohol use or inhaled or injection drugs, in the year prior to screening is exclusionary.

I. Use of other medications and supplements

35. Has the patient used any antidiabetic medications in the past 6 months:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	36.
	50.

(If yes, check all that apply):

- **a.** Metformin (Glucophage, Glucophage XR):
- **b.** Acarbose (Precose):
- c. Acetohexamide (Dymelor):
- **d.** Chlorpropamide (Diabinese): (1)
- e. Glimepiride (Amaryl):
- **f.** Glipizide (Glucotrol, Glucotrol XL): (
- **g.** Glyburide (Micronase, DiaBeta, Glynase):
- **h.** Insulin: (₁)
- i. Miglitol (Glycet): (1)
- **j.** Nateglinide (Starlix):
- **k.** Pioglitazone (Actos):
- **I.** Repaglinide (Prandin): (1)
- m. Rosiglitazone (Avandia):

 n. Tolazamide (Tolinase):
- o. Tolbutamide (Orinase):
- **p.** Other, (specify):

36. Has the patient taken any cardiovascular/antihypertensive medications in the past 6 months:

Yes	$\binom{\text{No}}{2}$
(1)	37.

(If yes, check all that apply):

a. Ar	mlodipine besylate (Norvasc):	(1)
b. As	spirin - 81 mg:	(1)

m. Hydrochlorothiazide (Esidrix,		
HydroDIURIL):	(1

n. Hydrochlorothiazide + triamterene	
(Dyazide):	(

o. Lisinopril (Prinivil, Zestril):	(1)
------------------------------------	---	----

q. Losartan potassium with		
hydrochlorothiazide (Hyzaar):	(1)

r. Metoprolol (Lopressor):	(1

ab. Other, (specify):	(1)

37. Has the patient taken any antihyperlipidemic medications in the past 6 months:

Y	es	N	lо
(1)	(2)
	Г	38. —	_

(If yes, check all that apply):

38. Has the patient taken any vitamins in the past 6 months:

Yes	No
$\begin{pmatrix} & & 1 \end{pmatrix}$	(₂)
	39.

(If yes, check all that apply):

1)

39. Has the patient taken any supplements in

rias the patient taken any supplements	111
the past 6 months:	
$\binom{\mathrm{Yes}}{1}$	No
(₁)	(2)
	40.
(If yes, check all that apply):	
a. Alpha-lipoic acid:	(1)
b. Alpha-tocopherol:	(1)
c. Beta-carotene:	(1)
d. Betaine (Cystadane):	(1)
e. Calcium (any form):	(1)
f. Carnitine (any form):	(1)
g. Chondroitin (any form):	(1)
h. Choline + methionine + betaine +	
adenosine + pyridoxine (Epocler):	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
i. Cod liver oil:	(1)
j. Coenzyme Q:	(1)
k. Dichloroacetate:	(1)
I. Echinacea:	()

40. Has patient taken any of the following medications or other supplements/medications in the past 6 months:

Yes	,	N	۱o ر
(1)	(2
	4	1.	_

(If yes, record all other supplements/medications):

- a. Isotretinoin (Accutane):
- **b.** Levothyroxine (Levoxyl, Synthroid):
- **c.** Liothyronine (Cytomel):
- d. Penicillamine (Cuprimine, Depen):
- e. Trientine hydrochloride (Syprine):
- **f.** Other, (specify):
- **g.** Other, (specify):
- **h.** Other, (specify):
- i. Other, (specify):
- **j.** Other, (specify):
- **k.** Other, (specify):

ab. Other, (specify):	(1)
aa. Other, (specify):	(1)
z. Zinc picolinate:	(1)
y. Taurine:	(1)
x. St. John's Wort:	(1)
w. Selenium:	(1)
v. Saw palmetto:	(1)
u. Potassium (any form):	(1)
t. N-acetyl-cysteine:	(1)
s. Magnesium:	(1)
r. Lecithin:	(1)
q. Glucosamine (any form):	(1)
p. Ginkgo biloba:	(1)
o. Garlic:	(1)
n. Flax seed oil:	(1)
m. Fish oil (any form):	(1)
I. Echinacea:	(1)
k. Dichloroacetate:	(1)
j. Coenzyme Q:	(1)
i. Cod liver oil:	(1)
h. Choline + methionine + betaine + adenosine + pyridoxine (Epocler):	(1)
g. Chondroitin (any form):	(1)
f. Carnitine (any form):	(1)
e. Calcium (any form):	(1)
d. Betaine (Cystadane):	(1)
c. Beta-carotene:	(1)
b. Alpha-tocopherol:	(1)
a. Alpha-lipoic acid:	(1)
(If yes, check all that apply):	40.	

T	A d	mir	ictr	ativa	infor	mation
J.	Au	mir	HSUT:	ative	intor	mation

day

41.	Study Physician PIN:	 	
42.	Study Physician signature:		
43.	Clinical Coordinator PIN:	 	
44.	Clinical Coordinator signature:		
45.	Date form reviewed:		

mon

year

BP - Blood Processing for Plasma and Serum

Purpose: Document collection of fasting blood for separation of plasma and serum.

When: Visits s, f12, f24, f36, f48, f60, f72 and f96.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of blood.

Instructions: Label tubes of blood using MACO labels specific for the patient and visit; these labels are generated by the clinical center upon registration (screening visit labels) or after enrollment (follow-up visit labels). Attach duplicate blood tube labels in items 11 and 13. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Label 2.0 mL cryovials with numbered patient-specific plasma (green-top) and serum (red-top) cryovial labels provided by the DCC. Affix plasma aliquot #00 label and serum aliquot #00 label to this form in item 18.

Screening and f72:

For plasma: Fill one 10 mL green top heparin tube with blood. Process blood for plasma within 30 minutes accordpipette 0.5 mL of plasma to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of plasma at -70 C. ing to procedures specified in the FLINT SOP I, section 6. After separation, prepare up to 10 aliquots of plasma:

For serum: Fill two 10 mL SST red-gray top tubes with blood. Process blood for serum within two hours according to procedures specified in the FLINT SOP I, section 6. After separation, prepare up to 20 aliquots of serum: pipette 0.5 mL of serum to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of serum at -70

Follow-up visits f12, f24, f36, f48, f60, f96:

For plasma: Fill one 10 mL green top heparin tube with blood. Process blood for plasma within 30 minutes according to procedures specified in the FLINT SOP I, section 6. After separation, prepare up to 10 aliquots of plasma: pipette 0.5 mL of plasma to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of plasma at -70 C.

For serum: Fill **one** 10 mL SST red-gray top tube with blood. Process blood for serum within two hours according to procedures specified in the FLINT SOP I, section 6. After separation, prepare up to 10 aliquots of serum: pipette 0.5 mL of serum to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of serum at -70 C.

NOTE: Immediately upon completion of plasma and serum aliquot preparation, destroy any leftover cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be able to be determined.

A. Center, patient and visit identification		B. Processing whole blood		
1. Center code:		Plasma and serum aliquots are to be separated from blood per instructions in the SOP I. Draw fasting blood in the morning.		
2. Patient ID:		8. Was participant fasting for at least 8 hours prior to blood draw: Yes No		
3. Patient code:		$ \begin{pmatrix} \text{Yes} & \text{No} \\ \text{1} & \text{*}_{2} \end{pmatrix} $ $ \boxed{23.} $		
4. Date of visit:		*Patient must be fasting.		
	mon year	 a. Was blood collected for the NIDDK Biosample Repository: 		
•	·	Yes (1)		
5. Visit code:		No, (specify): $(*_2)$		
6. Form & revision:	<u>b p 2</u>	23.		
7. Study:	FLINT 7	specify reason *If patient did not come to clinic for visit, complete the MV form instead of the BP form		
		9. Date and time of blood draw		
		a. Date:		
		day mon year b. Time:		
		$\phantom{aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa$		

Patient ID:	
I diffill ID.	

10. Number of heparin (green-top) tubes:	C. Aliquots for plasma and serum				
11. Affix matching heparin tube MACO label:	Pipette 0.5 mL of plasma into each of up to ten 2.0 mL pre-labeled cryovials and pipette 0.5 mL of serum into each of up to 20 (screening and f72) 10 (follow-up) 2.0 mL pre-labeled cryovials.				
FLINT Form BP, BP Plasma.	15. Date and time of separation into plasma and serum aliquots				
Pt: 9999, xyz Visit vvvv	a. Date: day mon year				
Date:	b. Time of plasma separation:				
12. Number of SST serum separator (red-gray top) tubes:	hour minute (1) (2) c. Time of serum separation:				
13. Attach duplicate SST serum separator tube labels:	hour minute (1) (2)				
FLINT Form BP, Serum 1 Pt: 9999, xyz Visit: vvvv BP	16. Number of aliquots for plasma: 17. Number of aliquots for serum:				
Date:	18. Attach duplicate cryovial labels (use aliquot #00 labels which are located in the first row of labels in the set):				
Needed during screening and f72 only FLINT Form BP, Serum 2 Pt: 9999, xyz Visit: vvvv BP Date:	Serum aliquot #00 label Plasma aliquot #00 label				
14. Phlebotomist:					
print name	19. Technician:				
	print name				

D. Freezing aliquots

Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK Biosample Repository at Fisher BioServices.

20. Date and time cryovials frozen in -70°C or -20°C

a Date

a. Date:			
	day	mon	vear

h Time:

. Time:			
hour	minute	(₁)	(pm 2

- **21.** Number of cryovials frozen: ____ ___
- **22.** Technician:

print name

E. Administrative information

- **23.** Clinical Coordinator PIN: ____ ___
- **24.** Clinical Coordinator signature:

25. Date form reviewed:

day mon year

FLINT

CG - Genetic Consent and Blood Collection Documentation

Purpose: To document options selected for use of blood samples for genetic research and the collection of whole blood for DNA extraction and banking at the NIDDK Genetics Repository at Rutgers University.

When: Screening visit s or as needed during follow-up due to a low yield (less than 50 g) of DNA (during follow-up, use the visit code of the follow-up visit that is open).

By whom: Study Physician, Clinical Coordinator and laboratory personnel responsible for collection of blood.

Instructions: Complete this form based on the consent documents signed by the patient. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG form. If the patient consents, (1) Apply MACO labels specific for the patient and visit to the EDTA vacutainer tubes; these labels are generated by the clinical center upon registration (screening labels). Affix duplicate tube label in item 18. (2) Fill two 10 mL EDTA vacutainer tubes with whole blood (see SOP I, section 6). (3) Pack the whole blood tubes in the specimen shippers supplied by the NIDDK Genetics Repository. Use the preprinted Federal Express shipping label, marked for Priority Overnight Delivery, to ship whole blood at ambient room temperature to the NIDDK Genetics Repository Monday-Friday on the same day it is collected.

A. Center, patient and visit iden	itification	9. For which study was it collected (check all that apply):		
1. Center ID:		a. Database	(1)
		b. PIVENS	(1)
2. Patient ID:		c. TONIC	(1)
3. Patient code:		d. Database 2	(1)
of fations code.		e. Other, (specify):	(1)
4. Date form completed:				
day m	non year	specify		
5. Visit code:			20.	
6. Form & revision:7. Study:	_cg1FLINT7_	10. Does the patient consent to genetic research on NAFLD or NASH-related cirrhosis that is currently planned by the study investigators: (Yes (1)	he	No 2)
B. Consent for collection, storag	ge, and use of blood	11 Does the natient consent to future gene	etic	

- B. Consent for collection, storage, and use of blood samples for current and future genetic research
 - 8. Has a sufficient yield of DNA (≥100 micrograms) been banked at the NIDDK Genetics Repository for this participant in a previous NASH CRN study:



11. Does the patient consent to future genetic research on NAFLD or NASH-related cirrhosis by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

12. Does the patient consent to future genetic research not related to NAFLD or NASH-related cirrhosis by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

13. Other information related to consent for genetic research that clinic staff feel needs to be keyed to the study database (e.s.

needs to be keyed to the study database (e.g., if your genetic consent had other options that are not covered by the 3 categories of use of samples specified above):

14. In your judgment, has the patient consented to collection of blood for DNA

banking (this question is asked in recognition that not all IRBs will have approved consent statements that include language that can be mapped into the questions in items 10 through 12; a response of "No" to this question (item 14) means that blood should NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):

C. Specimen for Genetics Repository

Attach ID labels to two 10mL EDTA tubes and fill each with blood; invert each tube gently 6 times to mix blood with additives; keep tubes at room temperature until the same day shipment to the NIDDK Genetics Repository.

15. Was blood collected today for the NIDDK Genetics Repository:

Yes

No, (specify):

specify

- 16. Date and time of blood draw
 - a. Date:

		_		_	
	day		mon		year
b. Time:					
	:_		(1)	(2)
ho	ur	minute	`	am	pm

17. Number of 10 mL EDTA tubes:

18. Attach form copy of tube label:

FLINT Form CG
Pt: ccc- 9999, xyz
Gender
Age, yrs.: XX

19. Phlebotomist:

print name

D. Administrative information

- **20.** Study Physician PIN:
- 21. Study Physician signature:
- **22.** Clinical Coordinator PIN: ____ ___
- 23. Clinical Coordinator signature:
- **24.** Date form reviewed:

	=	
day	mon	year

FLINT

CO - Closeout Form

Purpose: To close out a patient's participation in FLINT and document the patient's consent to join or re-enter the NAFLD Adult Database 2 study.

When: At f96 visit or at the close of the f96 window.

Respondent: Clinical coordinator.

Instructions: Complete this form for each patient randomized in FLINT at the f96 visit or at the close of the f96 window. Determine if the patient now wants to re-enter or join the NAFLD Adult Database 2. Schedule the patient for a NAFLD Adult Database 2 follow-up visit approximately 12 months from this visit.

- (1) Patients previously enrolled in the NAFLD Adult Database 2: consult the NAFLD Adult Database 2 visit schedule generated at NAFLD enrollment and use the visit window that is open in 12 months.
- (2) Patients NOT previously enrolled in the NAFLD Adult Database 2: if patient is willing to join the NAFLD Adult Database 2, a visit schedule will be generated upon keying this form. Schedule the participant approximately 12 months from their FLINT f96 visit for their t144 NAFLD Adult Database 2 follow-up visit.

A. C	enter,	patient	and	visit	identi	ficati	on
------	--------	---------	-----	-------	--------	--------	----

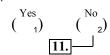
- 1. Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- **4.** Date of visit:

day	mon	year

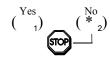
- **5.** Visit code: <u>f</u> <u>9</u> <u>6</u>
- **6.** Form & revision: <u>c o 1</u>
- **7.** Study: FLINT <u>7</u>

B. Database participation

8. Does the patient wish to re-enter or join the NAFLD Adult Database 2:

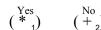


9. Has the patient signed the latest version of the NAFLD Adult Database 2 informed consent:



* Patient must sign the informed consent

10. Was the patient enrolled in the NAFLD Adult Database 2 previously:



* Schedule the patient's next NAFLD Adult Database 2 follow-up visit approximately 12 months from the date in item 4. Consult the patient's NAFLD Database 2 visit schedule and use the NAFLD Adult Database 2 visit open on that date. + Data system will generate a visit window schedule assigning the FLINT randomization date as the NAFLD Adult Database 2 enrollment date. Schedule the patient approximately 12 months from the date in item 4 for their t144 NAFLD Adult Database 2 follow-up visit.

C. Administrative information

- 11. Clinical Coordinator PIN:
- **12.** Clinical Coordinator signature:

13. Date form reviewed:

day	mon	year

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee.

By whom: Data Coordinating Center staff.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

	A. Clinic, patient and visit identification 1. Center ID
	2. Patient ID
	3. Patient code
////	4. Date of central reading
	5. Visit code
<u>c r 2</u>	6. Form and revision
<u> </u>	7. Study: 6 =Database 2; 7 =FLINT
/////	8. Date of biopsy
	B. Slide sequence number9. Sequence number for a. H & E stained slide
	b. Masson's trichrome stained slide
	c. Iron stained slide
	C. Adequacy of biopsy 10. Biopsy length (mm)
	11. Tissue adequate: 0 =No → Request original slides from submitting clinic; 1 =Yes
	12. Followup with clinic (<i>Specify</i>):
D. His E stain 3. Steatosis (assume macro, e.g., large and small drople)	stology et)

13. Steatosis	(assume macro, e.g.,	large and s	mall droplet)
---------------	----------------------	-------------	---------------

__ ... a. Grade: **0**=<5%; **1**=5-33%; **2**=34-66%; **3**=>66%

__ ... b. Location: **0**=Zone 3 (*central*); **1**=Zone 1 (*periportal*); **2**=Azonal; **3**=Panacinar

... c. Type of macrovesicular steatosis: **0**=Predominantly large droplet; **1**=Mixed large and small droplet; 2=Predominantly small droplet

d. Microvesicular steatosis, contiguous patches: **0**=Absent; **1**=Present

Patient ID	D. Histology (cont'd)
14. Inflammation	
	nflammation: combines mononuclear, fat granulomas, and pmn foci:
	20x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag
b. Microgranulomas s	
c. Large lipogranulon	as seen: 0=No; 1=Yes
d. Amount of portal, of	hronic inflammation: 0 =None; 1 =Mild; 2 =More than mild
15. Liver cell injury	
	e → GOTO Item 15d; 1=Few; 2=Many
b. Severe ballooning j	
c. Classical balloon co	
	ages (Kupffer cells): 0=Rare/absent; 1=Many
f. Megamitochondria:	
	o rear of designing a rearrange
16. Mallory-Denk bodies:	0=Rare/absent; 1=Many
17. Glycogen nuclei: 0 =R	are/absent; 1=Present in patches
	ocytes: 0 =Not present; 1 =Focal, involving less than 50% of the hepatocytes; 2 =Diffuse,
involving greater than	or equal to 50% of the hepatocytes
19. Masson's trichrome	atain
	one → GOTO Item 20; 1a=Mild, zone 3 perisinusoidal (requires trichrome);
	the 3, perisinusoidal (does not require trichrome); 1c=Portal/periportal only;
	portal, any combination; 3 =Bridging; 4 =Cirrhosis
	osis grade: 0 =No perisinusoidal fibrosis present; 1 =Perisinusoidal fibrosis present that
requires a Massor	stain to identify; 2=Perisinusoidal fibrosis present that is visible on the H&E stain
	on of fibrosis: 0 =More predominance around or between portal areas; 1 =No portal or
central predomina	nce; 2=More predominance around/between central veins
20. Iron stain	
20. Iron stain	grade: 0 =Absent or barely discernible, $40x \rightarrow GOTO$ item $20c$;
	ble granules, 20x; 2 =Discrete granules resolved, 10x; 3 =Discrete granules resolved, 4x;
4=Masses visible	
	distribution: 0 =Periportal; 1 =Periportal and midzonal; 2 =Panacinar; 3 =Zone 3 or azonal
	ron grade: 0=None → GOTO item 21; 1=Mild; 2=More than mild
d. Nonhepatocellular	ron distribution: 0 =Large vessel endothelium only; 1 =Portal/fibrosis bands only, but
more than just in	arge vessel endothelium; 2 =Intraparenchymal only; 3 =Both portal and intraparenchymal
	OO NE MARKED O MARKED AND CHEEK OF THE ALL IN THE SECOND OF THE SECOND O
	99=Not NAFLD; 0=NAFLD, not NASH; 1a=Suspicious/borderline/indeterminate: Zone
3 pattern; 1b =Suspici	ous/borderline/indeterminate: Zone 1, periportal pattern; 2 =Yes, definite
22 Is cirrhosis present? 0	=No → GOTO item 25 ; 1=Yes
22. Is chimosis present: 0	10 V GOTO Rem 25, 1 105
23. Is this cryptogenic cir	hosis: 0=No → GOTO item 25; 1=Yes
	steatohepatitis etiology for cryptogenic cirrhosis:
	es (rule out cholate stasis): 0 =Absent; 1 =Present
	sis away from septa: 0=Absent; 1=Present
c. Hepatocyte balloon d. Megamitochondria	
	ngs: 0=Absent; 1=Present; Specify:
c. Other notable final	.50. 0 11000m, 1 11000m, opeony.
25 Other comments:	

FLINT

Cardiovascular Risk Factors

Purpose: To determine a patient's need for referral for cholesterol management based on the Adult Treatment Panel III (ATP III) cholesterol guidelines.

When: Visits s, f24, f48, f72, and f96.

Administered by: Clinic coordinator by interview with patient and medical chart review.

Instructions: Collect information by interview, chart review, and by transcribing data from the FLINT Physical Examination (PE), Laboratory Results (LR), and Baseline (BG) or Follow-up (HI) Medical History forms. The anthropometric, blood pressure, and laboratory values reported on this form should be those collected at the same visit.

Important: Key the CV form only after you have keyed the BG/HI, LR, and PE forms.

A. Center, patient, and visit identification

- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ _____
- **3.** Patient code: _____ ____
- 4. Date of visit:

_		_
day	mon	year

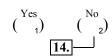
5. Visit code:

6	Form & revision:	C	17	1
о.	Form & revision:	C	V	- 1

7. Study: FLINT _7_

B. Smoking history

8. Is this the first time a smoking history has been obtained in FLINT on a CV form:



9. Have you ever smoked tobacco cigarettes:

Never	(1)
	15.
In the past, but not anymore	— (₂)
Currently smokes cigarettes	(* 3)

*The patient smoked at least one cigarette in past month.

10. Do you/did you smoke cigarettes regularly:



*Less than 2 packs of cigarettes in a lifetime or less than 1 cigarette a day for one year.

11. How old were you when you first started regular cigarette smoking:

years

12. How old were you when you (last) stopped smoking cigarettes (code as "n" if the patient did not stop smoking):

vears

13. On the average of the entire time that you smoked cigarettes, how many cigarettes did you smoke per day:

cigarettes/day

C. Framingham Risk Assessment

14. Are you a current cigarette smoker:

 $\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$

15. Gender

Male Female $\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$

16. Age:

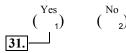
years

If lipid panel was not obtained, skip to item 27.	24. Framingham point scores (use the ATP III At-a-
17. Total cholesterol (from LR form):	Glance Quick Desk Reference [NIH Publication No. 01-3305] on page 5 to record gender-specific scores based on the patients risk factors. Circle
mg/dL	"+" or "-" as appropriate. Key "+#" or "-#"; if 0 for an item with +/-, key "+0" or "+00".)
If the patient has total cholesterol greater than 300 mg/dL, an IE form should be completed.	a. Age score (based on item 16): +/
	points
18. HDL cholesterol (from LR form):	b. Total cholesterol score (based on items 16 and 17):
${}$ mg/dL	points
	c. Smoking score
19. LDL cholesterol (from LR form)*:	(based on items 9 or 14, and 16):
	d. HDL score (based on
mg/dL	item 18): +/
*Enter "GT" if LDL cannot be calculated due to high triglycerides.	points
	e. Systolic blood pressure score (based on items 20 and 22):
20. Systolic blood pressure (from PE form):	points
mmHg	25. Point total (Add items 24a-e): + / points
21. Diastolic blood pressure (from PE form):	26. Framingham risk of heart attack or dying
1 0 7	of coronary heart disease in the next 10
mmHg	years (using the ATP-III at-a-glance publication on page 5, use the point total
22. Are you currently being treated for high blood pressure with medicine prescribed	[item 25] to convert into gender-specific 10 year risk):
by your doctor:	%
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	If 10 year risk < 1, record "00". If 10 year risk \geq 30, record "30".
23. Has anyone in your immediate family	
(blood-related parent, brother, sister, or	D. ATP III guidelines
child) been diagnosed with early heart disease (before age 55 years for male relatives and before 65 years for female	27. Have you been diagnosed with type 1 or type 2 diabetes:
relatives):	$\begin{pmatrix} \text{Yes} & \begin{pmatrix} \text{No} \\ 1 \end{pmatrix} & \begin{pmatrix} \frac{\text{No}}{2} \end{pmatrix} \end{pmatrix}$
$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	$\begin{pmatrix} 1 \end{pmatrix} \begin{pmatrix} 2 \end{pmatrix}$
(1) (2)	
	28. Have you been diagnosed with clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):
	$ \begin{pmatrix} Yes \\ \begin{pmatrix} 1 \end{pmatrix} \end{pmatrix} $
	29.]—
	(If yes, check all that apply)
	a. Clinical CHD: (1)

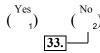
b. Symptomatic carotid artery disease:

c. Peripheral arterial disease:d. Abdominal aortic aneurysm:

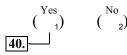
29. Was "Yes" checked for either item 27 or 28 or was LDL unknown ("GT" in item 19 or lipid panel not obtained):



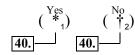
30. Is 10-year Framingham heart attack risk estimate 22% (item 26) or more:



31. Is LDL cholesterol (item 19) less than 100 mg/dL or was LDL unknown ("GT" in item 19 or lipid panel not obtained):



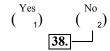
32. Is LDL cholesterol (item 19) 130 mg/dL or more:



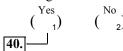
*Refer for cholesterol management with LDL-lowering drug therapy (see FLINT SOP V).

†Refer for cholesterol management with drug therapy optional, initiate LDL-lowering therapeutic lifestyle changes (see FLINT SOP V).

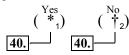
- **33.** Coronary heart disease (CHD) risk factors: Do you have any of the following:
 - a. Current cigarette smoking (see item 9 or 14):
 - **b.** SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or on antihypertensive medication (based on items 20, 21, and 22):
 - c. HDL cholesterol less than 40 mg/dL (based on item 18): (1)
 - **d.** Family history of premature CHD (see item 23):
 - e. Age in men \geq 45 years or age in women \geq 55 years (based on items 15 and 16):
 - f. HDL cholesterol 60 mg/dL or more (based on item 18):
- 34. Total number of CHD risk factors
 (add number of "yes" in items 33a-e and
 subtract 1 if item 33f is "yes"; code as
 "0" if only 33f is "Yes"):
- **35.** Are there 2 or more CHD risk factors (item 34):



36. Is LDL cholesterol less than 130 mg/dL:



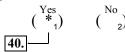
37. Is 10-year Framingham heart attack risk estimate between 10 and 20%, inclusive or LDL cholesterol 160 mg/dL or more:



*Refer for cholesterol management with LDL-lowering drug therapy (see FLINT SOP V).

†Refer for cholesterol management with drug therapy optional, initiate LDL-lowering therapeutic lifestyle changes (see FLINT SOP V).

38. Is LDL cholesterol 190 mg/dL or more:



*Refer for cholesterol management with LDL-lowering drug therapy (see FLINT SOP V).

39. Is LDL cholesterol between 160 and 189 mg/dL, inclusive:



†Refer for cholesterol management with drug therapy optional, initiate LDL-lowering therapeutic lifestyle changes (see FLINT SOP V).

E. Other cardiovascular events

40. Has the patient ever been diagnosed with or treated for any of the following *(check all that apply)*

a.	Myocardial	infarction:	(1)

	specify	

- F. Administrative information
- **41.** Study Physician PIN:
- **42.** Study Physician signature:
- **43.** Clinical Coordinator PIN:
- **44.** Clinical Coordinator signature:
- **45.** Date form reviewed:

mon

year

day

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total			Points		
Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
1 2 3 4 5 6	1
4	1
5	2
6	2
7	3
8	2 2 3 4 5 6
9	5
10	
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total			Points		
Cholesterol [Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
[Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Daint Tatal	10 V Pi-l- 0/
Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

FLINT

DR - Death Report

Purpose: To record the report of a patient's death.

When: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete this form whenever the clinical center is informed of a patient's death. If the death is considered associated or possibly associated with participation in the FLINT study, complete a Serious Adverse Event (SR) form and follow the directions on Form SR for reporting a serious adverse event in FLINT.

A. Center, patient, and visit ide	ntification		10. Place of death:	
1. Center ID:			city/state/country	
2. Patient ID:			city/state/country	
3. Patient code:4. Date form is initiated (date of the code)	f notice):		11. Cause of death (Study Physician: use whatever have and your best medical judgm acterize the cause of death; check	ent to best char-
			Heart disease	(_1)
day m	on yes	ar	Stroke	$\begin{pmatrix} & & & & & & & & & & & & & & & & & & &$
5. Visit code:	_n		Liver disease	$\begin{pmatrix} & 2 \\ & 3 \end{pmatrix}$
			Malignancy	(4)
6. Form & revision:	<u>d</u> <u>r</u>	_1_	Other (specify):	(5)
7. Study:	FLINT	_7_	specify	
B. Death information			specify	
8. Date of death:			Unknown	(6)
	on yes	ar	C. Administrative information	
9. Source of death report (check	k all that apply)	:	12. Study Physician PIN:	
a. Patient's family:	((1)		
b. Friend:	((1)	13. Study Physician signature:	
c. Health care provider or Na staff:	ASH CRN	(1)	14. Clinical Coordinator PIN:	
d. Newspaper:	((1)		
e. Funeral parlor/home:	((1)	15. Clinical Coordinator signature:	
f. Medical record:	((1)		
g. Medical examiner:	((1)	16. Date form reviewed:	
h. Coroner:		(1)		
i. Other (specify):	((1)	day mon	year
other sour	rce			
other sour	rce			

FLINT

HF - Liver Biopsy Histology Findings

Purpose: Record results of the histologic evaluation of slides from the liver biopsy for eligibility. **When**: Visit s.

By whom: Clinical Coordinator after Study Pathologist completed the Histology Worksheet (HW form).

Instructions: The Study Pathologist should complete the Histology Worksheet (HW) using the institution's H & E slide and if available, the institution's Masson's trichrome and iron slides. After completing the HW form, the Study Pathologist should give the worksheet to the Clinical Coordinator who will transcribe the data to the HF form and staple the worksheet to the HF form. If () is checked for any item, the patient is not eligible for FLINT and the form should not be keyed. If \(\subseteq \) is checked for an item, use caution; if the Study Physician agrees with the diagnosis, the patient is ineligible for FLINT and the form should not be keyed.

If fewer than 3 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 3 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the DCC.

A. Center, patient and visit identific	cation	C. NASH evaluation (use H & E and Masson's trichrome slides only)		
1. Center ID:		1.1455011 5 4110111 01110 011405 01113)		
2. Patient ID:		11. Steatosis (assume macro, e.g., large droplet)	and small	
Z. I diferit ID.		a. Grade:		
3. Patient code:		< 5%	(₀)	
4. Date of visit:		5-33%		
4. Date of visit:		34-66%	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	
day mon	year	> 66%	$\begin{pmatrix} & 2 \\ & 3 \end{pmatrix}$	
		b. Location:	. 0	
5. Visit code:	_S	Zone 3	(0)	
		Zone 1	$\begin{pmatrix} 1 \end{pmatrix}$	
6. Form & revision:	_hf2_	Azonal	(2)	
	ELINE 7	Panacinar	(3)	
7. Study:	FLINT 7	12. Fibrosis stage (Masson's trichrome sto	ain)	
D. D'		- ,	,	
B. Biopsy information		0: None	(0)	
8. Date this biopsy was performed <i>surgical pathology report):</i>	(obtained from	1a: Zone 3, perisinusoidal (requires trichome)	(1)	
day mon		1b: Zone 3, perisinusoidal (easily seen on H & E)	(₂)	
day	year	1c: Portal/periportal only	$\begin{pmatrix} & 2 \\ & 3 \end{pmatrix}$	
9. What slides are to be used in this evaluation <i>(check all that apply)</i>	S	2: Zone 3 and periportal, any combination	(4)	
a. H & E:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	3: Bridging	(5)	
b. Masson's trichrome:	(1)	4: Cirrhosis	(6)	
c. Iron:	(1)		(Elig)—	
10. Biopsy length:	 mm			

13. Inflammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:



< 2 / 20x mag

2-4 / 20x mag

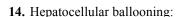
> 4 / 20x mag

b. Amount of portal, chronic inflammation:

None to minimal

Mild

More than mild



None



Few

Many

1)

15. Is steatohepatitis present:

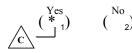


Suspicious/borderline/indeterminate

Yes, definite

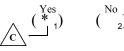
D. Exclusion of other liver disease

16. Is there evidence of primary biliary cirrhosis:



* Caution: Primary biliary cirrhosis is exclusionary

17. Is there evidence of Wilson's disease:



* Caution: Wilson's disease is exclusionary

18.	Features of chronic cholestatic liver
	disease (check all that apply)

a. Bile duct loss/infiltration/sclerosis:



b. Florid duct lesions:

c. Cholate stasis:

d. Copper deposition:

e. Other (specify):

f. None:

* Caution: Bile duct obstruction and primary sclerosing cholangitis are exclusionary

19. Features of other forms of chronic liver disease (check all that apply)

a. Vascular lesions of ALD/B-C/OVD:

b. Inflammation suggestive of AIH, HCV:



c. Pigment suggestive of HH:



d. Globules suggestive of A1AT:



e. Hepatocellular changes suggestive of

HBV:



f. Granulomas suggestive of sarcoid,

PBC, infection:



g. Other (specify):

h. None:

* Exclusionary

E. NAFLD Activity Score

20. NAFLD activity score (NAS) (sum of items 11a, 13a, and 14)

3-8

(Note: each subscore must be 1 or more)

21. Is item 20 (NAS) 3 or less:



F. Other comments

22. Other comments:

G. Administrative information

- **23.** Study Pathologist PIN:
- **24.** Study Pathologist signature (Pathologist does not need to sign this form if a signed HW form is attached.):

- **25.** Clinical Coordinator PIN: ____ ___
- **26.** Clinical Coordinator signature:
- **27.** Date form reviewed:

_		_
day	mon	year

FLINT

HI - Follow-up Medical History

Purpose: To record follow-up medical history information about the patient. When: Visits f02, f04, f12, f24, f36, f48, f60, f72, f96.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview and chart review.

Α.	Center.	visit.	and	natient	identification
A.	Cuitti,	V 131t	anu	paucit	iuciitiitatioii

- 1. Center ID:
- 2. Patient ID:
- 3. Patient code:
- **4.** Visit date (date this form is initiated):

_		_
day	mon	year

- **5.** Visit code:
- <u>h</u> i 2 **6.** Form & revision:
- FLINT 7 7. Study:

B. Interval identification

8. Date of last Follow-up Medical History form (if this is visit f02 then date of s):

=_		
day	mon	year

9. Visit code of last Follow-up Medical History form (if this is visit f02 then s):

C. NAFLD evaluation

10. Has the participant had a liver biopsy since the last visit:

D. Alcohol consumption (AUDIT-C) since the last visit

11. Since the last visit, how often have you had a drink containing alcohol:

Never	()
	14.
Monthly or less	(
Two to four times a month	(2)
Two to three times a week	(3)
Four or more times a week	(4)

12. Since the last visit, how many drinks containing alcohol have you had on a typical day when you are drinking:

1 or 2	(,	0)
3 or 4	(1)
5 or 6	(2)
7 to 9	(.	3)

10 or more 13. Since the last visit, how often have you

had six or more drinks on one occasion:

Never Less than monthly Monthly

Weekly

Daily or almost daily

^{*}Complete the Liver Biopsy Materials Documentation (SD) form.

E. R	ecent medical history			aa. Short bowel syndrome:	(1)
14. Has the patient been diagnosed with any		ab. Hemophilia (bleeding disorder):	(1)		
	of the following since the last visit (check			ac. HIV positive:	(1)
	apply; source of information can be in and/or chart review)	iterv	riew	ad. Systemic autoimmune disorder such		
	a. Diabetes type 1:	(.)	as rheumatoid arthritis or systemic lupus:	(1)
	b. Diabetes type 2:	(1) 1)	ae. Endocrine disease	(1)
	c. Chronic hepatitis B:	$\tilde{}$	1)	(hormonal abnormality):	(1)
	d. Hepatitis C:	\mathcal{L}	1)	af. Hepatocellular carcinoma:	(1)
	e. Active autoimmune hepatitis:	\mathcal{L}	1)	ag. Other malignancy (cancer):	(1)
	f. Autoimmune cholestatic liver disorder	(1)	ah. Peripheral neuropathy:	(1)
	(PBC):	(1)	ai. Seizure disorder or epilepsy:	(1)
	g. Wilson's disease:	(1)	aj. Drug allergies:	(1)
	h. Alpha-1-antitrypsin (A1AT)	Ì	12	ak. Hypothyroidism:	(1)
	deficiency:	(1)	al. Hypertension:	(1)
	i. Glycogen storage disease:	(1)	am. Cerebrovascular disease:	(1)
	j. Iron overload:	(1)	an. Chronic cholestasis:	(1)
	k. Hemochromatosis:	(1)	ao. Hyperlipidemia (high cholesterol,		
	l. Polycystic liver disease:	(1)	high triglycerides):	(1)
	m. Biliary diversion:	(1)	ap. Pancreatitis:	(1)
	n. Primary sclerosing cholangitis:	(1)	aq. Cholelithiasis:	(1)
	o. Drug induced liver disease:	(1)	ar. Coronary artery disease:	(1)
	p. Bile duct obstruction:	(1)	as. Congestive heart failure:	(1)
	q. Gilbert's syndrome:	(1)	at. Elevated uric acid such as gout:	(1)
	r. Esophageal or gastric varices on	,	`	au. Kidney disease:	(1)
	endoscopy:	(1)	av. Polycystic ovary syndrome:	(1)
	s. Bleeding from varices:	(1)	aw. Sleep apnea (not breathing	(`
	t. Other gastrointestinal bleeding:	(1)	during sleep):	(1)
	u. Ascites:	(1)	ax. Dermatologic disorders:	(1)
	v. Edema:	(1)	ay. Myopathy:	(1)
	w. Hepatic encephalopathy:	(1)	az. Myositis:	(1)
	x. Portal hypertension:	(1)	ba. Major depression:	(1)
	y. Hepatorenal syndrome:	(1)	bb. Schizophrenia:	(1)
	z. Hepatopulmonary syndrome:	(1)	bc. Bipolar disorder:	(1)
				bd. Obsessive compulsive disorder:	(1)
				be. Severe anxiety or personality disorder:	(1)
				bf. Substance abuse:	(1)
				bg. Other (specify):	(1)
				specify		—
				bh. None of the above:	(1)

15.	Since the last visit, has the patient had		F. Drugs historically associated with NAFLD		
	surgery for any of the following (check all that apply)		20. Has the patient used any of the following since last visit:		
	a. Stapling or banding of the stomach: (1)	Yes (Yes	N	lo 、
	b. Jejunoileal (or other intestinal) bypass: (1)	(1)	(2)
	c. Biliopancreatic diversion:	1)	21.	-	J
	d. Other GI or bariatric surgery (specify):	1)	(If yes, check all that apply):	,	`
			a. Amiodarone (Cordarone, Pacerone):	(1)
	e. None:		b. Demeclocycline (Declomycin):	(1)
16	Is the patient currently undergoing	17	c. Divalproex (Depakote):	(1)
10.	evaluation for bariatric surgery:		d. Doxycycline (Monodox):	(1)
	$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix}$	No	e. Methotrexate (Rheumatrex):	(1)
		2)	f. Minocycline (Dynacin, Minocin):	(1)
17.	Since the last visit, has the patient		g. Oxytetracycline (Terramycin):	(1)
	received:		h. Tetracycline (Achromycin):	(1)
	a. Liver transplant: Yes 1	No)	i. Valproate sodium (Depacon):	(1)
	b. Any other organ, limb, or bone	2)	j. Valproic acid (Depakene):	(1)
	marrow transplant		k. Other known hepatotoxin #1 (specify):	(1)
	Yes (1)	No 2			
10	Since the last visit, has the patient had	2)	I. Other known hepatotoxin #2 (specify):	(1)
10.	ER visite or hospitalizations:				
	Yes (*1) (No 2)	m. Other known hepatotoxin #3 (specify):	(1)
	* Complete an Interim Event Report (IE) form If Yes, specify reason and list dates:	<i>n</i>	21. Has the patient taken any systemic glucocorticoids since last visit: (Yes (1) (22)	(N	lo 2)
			(If yes, check all that apply):		
	TA A		a. Betamethasone sodium (Celestone):	(1)
	If none for items 18a or 18b, enter "00".		b. Cortisol:		.)
	a. Number of hospitalizations:		c. Cortisone:		.)
	# of hospital	izations	d. Dexamethasone (Decadron):	(1) 1)
	b. Number of Emergency Room visits:		e. Hydrocortisone (Hydrocortone):		1)
	# of vis	its	f. Methylprednisolone (Solu-Medrol):	(1)
19.	Since the last visit, has the patient had		g. Prednisolone (Prelone):	\tilde{c}	1)
	any serious health problem or adverse		h. Prednisone:	\tilde{c}	1)
	events not already reported:	No	i. Triamcinolone (Acetocot, Amcort,	(17
	Yes (* 1)	2)	Aristocort, Kenacort):	(1)
	20.		j. Other, (specify):	(1)
	* Complete an Interim Event Report (\overline{IE}) form	n			
	If Yes, specify and list dates:		k. Other, (specify):	(1)

22. Has the patient taken any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective estrogen receptor modulators since last visit:

Yes (1)	$\binom{No}{2}$
	23.

(If yes, check all that apply):

- **a.** Boldenone undecylenate (Equipoise):
- **b.** Conjugated estrogen (Premarin/Prempro): (1)
- **c.** Diethylstilbestrol and methyltestosterone (Tylosterone):
- **d.** Esterified estrogen (Estratab, Menest): $\begin{pmatrix} 1 \end{pmatrix}$
- e. Estradiol (Estrace):
- **f.** Ethinyl estradiol (Estinyl):
- **g.** Fluoxymesterone (Android-F, Halotestin):
- **h.** Levonorgestrel (Norplant): $\binom{1}{1}$
- i. Medroxyprogesterone (Cycrin, Provera):
- j. Megestrol (Megace):
- **k.** Methandrostenolone (Dianabol):
- **l.** Methyltestosterone (Android): (1)
- **m.** Nandrolone (Deca-Durabolin, Durabolin, Hybolin Decanoate, Kabolin):
- **n.** Norethindrone (Micronor):
- o. Norgestrel (Ovrette):
- p. Oral contraceptives (Alesse, Demulen, Desogen, Estrostep, Genora, Intercon, Levlen, Levlite, Levora, Loestrin, Lo-Ovral, Necon, Nelova, Nordette, Norethin, Norinyl, Ortho Cyclen, Ortho-Novum, Ortho Tri-Cyclen, Ovral, Tri-Levlen, Triphasil, Trivora, Zovia):
- Zovia): $\begin{pmatrix} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ \end{pmatrix}$ Q. Oxandrolone (Oxandrin): $\begin{pmatrix} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ \end{pmatrix}$
- r. Oxymetholone (Anadrol):
- s. Progesterone (Prometrium):
- t. Raloxifene (Evista):
- u. Stanzolol (Winstrol):
- v. Tamoxifen (Nolvadex):
- w. Testosterone (Depo-Testosterone):
- **x.** Other, (specify):

y. Other, (specify):	(1)

G. Use of antiNASH drugs and supplements

23. Has the patient taken any of these antiNASH drugs since last visit:

Yes (1)	(No 2)
	24.	J

(If yes, check all that apply):

- a. Betaine (Cystadone):
- **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler):
- **c.** Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
- **d.** S-adenylmethionine (SAM-e):
- e. Milk thistle:
- **f.** Probiotics (any form):
- **g.** Other (specify):

specify

24. Has the patient taken a thiazolidinedione since last visit:

Y	es	N	О
(1)	(2)

H. Use of antiobesity drugs

25. Has the patient taken any antiobesity medications since last visit:

Yes		N	Jo ر
(1.)	(2)
	26.		J

(If yes, check all that apply):

- a. Dexfenfluramine hydrochloride (Redux):
- **b.** Fenfluramine hydrochloride (Pondimin):
- c. Methamphetamine hydrochloride (Desoxyn, Gradumet):
- **d.** Orlistat (Xenical):
- e. Phendimetrazine tartrate (Adipost, Bontril):
- **f.** Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
- g. Sibutramine hydrochloride monohydrate (Meridia):
- h. Other, (specify):
- i. Other, (specify):

I. Use of antidependency drugs

26. Has the patient taken any alcohol abuse, inhaled or injection drugs (dependence or withdrawal) medications since last visit:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	27.

(If -1, -1, -11 +1, -+ ----1-.)

(IJ yes, check all that apply):		
a. Chlordiazepoxide (Librium):	(1
b. Clorazepate dipotassium (Tranxene):	(1.
c. Diazepam (Valium):	(1.
d. Disulfiram (Antabuse):	(1.
e. Hydroxyzine pamoate (Vistaril):	(1
f. Naltrexone hydrochloride (Revia):	(1
g. Other, (specify):	(1.

J. Use of other medications and supplements

27. Has the patient used any antidiabetic medications since last visit:

Yes (1)	$\binom{\text{No}}{2}$
	28.

(If yes, check all that apply):

a. Metformin (Glucophage, Glucophage

XR):	(1)
b. Gemfibrozil (Gen-Fibro, Lopid):	VOII
c. Acarbose (Precose):	(1)
d. Acetohexamide (Dymelor):	(1
e. Chlorpropamide (Diabinese):	(1
f. Glimepiride (Amaryl):	(1
g. Glipizide (Glucotrol, Glucotrol XL):	(1

h. Glyburide (Micronase, DiaBeta,		
Glynase):	(1)
i. Insulin:	(1)

i. Insulin:	(1)
j. Miglitol (Glycet):	(1)
k. Nateglinide (Starlix):	(1)
1 D: 1': (A :)	(

1. Plogittazone (Actos).	(1.
m. Repaglinide (Prandin):	(1
n. Rosiglitazone (Avandia):	(1

n.	Rosiglitazone (Avandia):	(1
0.	Tolazamide (Tolinase):	(1

p.	Tolbutamide (Orinase):	(1
a.	Other (specify):	(

28.	Has the patient taken any
	cardiovascular/antihypertensive
	medications since last visit:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	29.

(If yes, check all that apply):

a. Amlodipine besylate (Norvasc):	(1)
b. Aspirin - 81 mg:	(1)
c. Atenolol (Tenormin):	(1)

n. Hydrochlorothiazide + triamterene		
(Dyazide):	(1)

	(Dyuziuc).	(1/
0.	Lisinopril (Prinivil, Zestril):	(1)

w. Terazosin (Hytrin):
$$\begin{pmatrix} 1 \end{pmatrix}$$

x. Timolol maleate (Blocadren):
$$\binom{1}{1}$$

29. Has the patient taken any antihyperlipidemic medications since last visit:

Yes	No
(1)	(2
	30.

(If yes, check all that apply):

(1)
(1)
(1)
(1)
(1)
(1)
(1)
(1)
(1)
(1)
(1)
(1)

30. Has the patient taken any vitamins since last visit:

Yes (1)	$\binom{\text{No}}{2}$
	31.

(If yes, check all that apply):

a. Vitamin B (any type):	(1
b. Vitamin C:	(1.
c. Vitamin D:	(1
d. Vitamin E:	(1
e. Multivitamin:	(1
f. Other, (specify):	(1.

31. Has the patient taken any supplements since last visit:

Yes	No	No		
$\begin{pmatrix} 1 \end{pmatrix}$	(2)		
	32.			

(If yes, check all that apply):

a. Alpha-lipoic acid:	(1)
b. Alpha-tocopherol:	(1)

i.	Cod liver oil:	(. 1
	0		٠ ,

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32. Has patient taken any of the following medications or other supplements/medications since last visit:

Yes ((No 2)
	3	3.	J

1)

(If yes, record all other supplements/medications):

- a. Isotretinoin (Accutane): (
- b. Levothyroxine (Levoxyl, Synthroid): (1)c. Liothyronine (Cytomel): (1)
- **d.** Penicillamine (Cuprimine, Depen):
- e. Trientine hydrochloride (Syprine):
- **f.** Other, (specify):
- g. Other, (specify):
- **h.** Other, (specify):
- i. Other, (specify):
- **j.** Other, (specify): ($_{1}$)
- **k.** Other, (specify):

- K. Administrative information
- **33.** Study Physician PIN:
- **34.** Study Physician signature:

36. Clinical Coordinator signature:

- **35.** Clinical Coordinator PIN:
- **37.** Date form reviewed:

	_	_	
day	mon	ye	ear

IE - Interim Event Report

Purpose: To document an adverse event that threatens the integrity of the FLINT trial or well-being of a study participant that includes, but not limited to:

- (1) events that impact the patient's treatment or participation in FLINT
- (2) adverse events that are recorded on the Follow-Up Medical History (HI) form
- (3) adverse events that may or may not be related to study drug
- (4) other events that clinical center staff feel should be reported
- (5) when a follow-up report is needed for a previously completed IE form

As defined by Title 21 Code of Federal Regulations Part 312.32 *IND Safety Reporting*: *Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other medical events may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

When: As needed. Use visit code if reporting an event discovered during a regular follow-up visit. Use visit code n if event is discovered between study visits. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code for first event, n for second event, n2 for third event, etc. Adverse events that are serious, unexpected and have reasonable possibility of being caused by FLINT study drug should also be recorded on the Serious Adverse Event/IND Safety Report (SR) form.

Completed by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 16) and the severity grade (item 17) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Studies and then FLINT. Fax the DCC (Fax 410-955-0932; Attention: Ivana Vaughn) a copy of this form if severity grade is 3 or higher within 1 week for further review by Dr. Jeanne Clark, the NASH CRN Safety Officer. For more information, see SOP I sections 6.15 and 6.16.

Follow-up report: A follow-up report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patient's condition or in the physician's judgment about the event since the previous report was filed.

A. Center, patient, and visit identification		5. Visit code: if report not associated with a visit, fill in "n"		
1. Center ID:		y .1.	, , , , , , , , , , , , , , , , , , ,	
		6. Form & revision:	<u>i e 3</u>	
2. Patient ID:				
		7. Study:	FLINT <u>7</u>	
3. Patient code:				
4. Date of report:				
day mon	year			

B. Visit interval identification			14. Describe event:		
8. Most recently completed visit (screening or followup)	g				
a. Date:	year				
b. Visit code:					
C. Patient information			,		
9. Gender: Male	(1)	For items 15, 16, and 17, please refer to CT available at www.nashcrn.com; click on Studthen FLINT.		
Female	(1) 2)			
		2)	15. Identify body system (check all that app	oly)	
10. Age at time of event:	years		a. Auditory/ear:	(1)
	J		b. Allergy/immunologic:	(1)
D. Event description			c. Ocular/visual:	(1)
11. Is this the first report or a followup repo	ort		d. Hepatobiliary/pancreatic:	(1)
for this adverse event:	,	`	e. Infection:	(1)
First report	(1)	f. Constitutional symptoms:	(1)
Followup report	(2)	g. Psychiatric:	(1)
12. Date event started:			h. Cardiovascular:	(1)
<u> </u>			i. Dermatologic/skin:	(1)
day mon	year		j. Endocrine/metabolic:	(1)
13. Nature of event <i>(check all that apply)</i>			k. Gastrointestinal/digestive:	(1)
a. Drug dispensing mixup:	(1)	l. Lymphatic/blood:	(1)
b. Medication related event:	(1)	m. Musculoskeletal:	(1)
c. Study procedure related event:	(1)	n. Neurologic:	(1)
d. Severe allergic reaction:	(1)	o. Pulmonary/respiratory:	(1)
e. Drug interactions:	(1)	p. Renal/genitourinary:	(1)
f. Worsening of a co-morbid illness:	(1)	q. Sexual/reproductive:	(1)
g. Patient reported symptom of hepatotoxicity:	(1)	r. Other (specify):	(1)
h. Hypoglycemia/hyperglycemia:	(1)	specify other body system		—
i. Diabetes:	(1)	s. None of the above:	(1)
j. Pregnancy (patient):	(*1)			17
k. Other (specify):	(1)	16. Short name for event if applicable:		
			Not applicable	(0)

^{*}FLINT study drug will be discontinued if a patient becomes pregnant. Contact the NASH CRN Data Coordinating Center to unmask the study drug.

17. Severity grade:			22. Is this a serious adverse event:
Not an adverse event	(0	$\begin{pmatrix} \text{Yes} & \text{No} \\ 1 & \end{pmatrix}$
Grade 1 - Mild	(1)	23.
Grade 2 - Moderate	(2)	If Yes, then select all the reasons that apply:
Grade 3 - Severe	(3)	a. Severity Grade 4 or 5:
Grade 4 - Life threatening or disabling	(4)	b. Required inpatient hospitalization or
Grade 5 - Death	(* ₅)	prolonged existing hospitalization: (1)
*Complete and key Death Report (DR) form 18. Randomization in FLINT	n.		c. Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions:
a. Has patient been randomized in FLINT:			d. Jeopardized patient and required medical or surgical intervention to prevent a serious event:
(Yes 1) 26.	(N	No 2)	e. Congenital abnormality or birth defect: (1)
b. Date randomized in FLINT:			23. Is this an unexpected adverse event:
day mon y	ear		$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$
19. Is the patient currently receiving the			<u> </u>
FLINT study drug:	N	No 2)	24. Reason the adverse event was unexpected:
20. Patient's history of treatment with	(2)	Not listed in the obeticholic acid investigator's brochure (1)
FLINT study drug a. How long has patient been on study drug:			Listed in the obeticholic acid investigator's brochure, but not at the specificity or severity that has been observed
b. Have there been any treatment interruptions or restarts: (Yes (1) Include stop/restart dates and reasons:	(^N	No 2)	Listed in the obeticholic acid investigator's brochure as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with previous experience of obeticholic acid (3)
			25. Did you select "Yes" for items 21 (definitely, probably, or possibly), 22, and 23:
21. Is there evidence to suggest a causal relationship between the FLINT study drug and the adverse event:		_	Yes No (*1) (2) *If Yes, please also complete a Serious Adverse Event/IND Safety Report (SR) form and follow instructions.
Definitely yes	(1)	26. Current status of adverse event <i>(check only one):</i>
Probably yes	(2)	Resolved (4)
Possibly yes	(3)	Active (2)
Probably no	(4)	\ \
Definitely no	(5)	Unknown (3)

Patient	ID.		

27. Date adverse event resolved:			E. Administrative information		
_		mon	year	30. Clinical Coordinator PIN:	
28. What action was taken:			31. Clinical Coordinator signature:		
				32. Study Physician PIN:	
				33. Study Physician signature:	
29. Other con	nments on e	event:		34. Date form reviewed:	
				day mon year	
			Key this form and fax the DCC (Attention: Ivana Vaughn) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious adverse events so that we assure appropriate and timely study wide review. The serious adverse event reports will be reviewed by Dr. Jeanne Clark, the Safety Officer.		

LD – Lifetime Drinking History (Skinner)

Keyed: ()

Purpose: To obtain quantitative indices of the patient's alcohol consumption patterns from the onset of regular drinking.

When: Visit s. If more than one LD form is needed, use visit code "n" on the second LD form.

Administered by: Clinical Coordinator.

Respondent: FLINT Patients, without help from spouse or family.

Instructions: In addition to actual consumption levels (quantity), attention is focused upon the frequency of use, variability in consumption, types of beverages, life events that mark a change in drinking pattern, solitary versus social drinking, and time of day when alcohol is consumed. Flash Card #9, Drink Equivalents, may be used with this interview.

The interviewer begins by recording the patient's alcohol consumption behavior during the first year that he/she drank on a regular basis (at least one drink per month). Then, the patient is asked to think of when his/her drinking behavior changed in any appreciable way. In a chronological fashion, the interviewer traces the patient's alcohol consumption behavior from the age of first regular drinking to the present. Flash Card #10, Patterns of Alcohol Intake, provides sample language for the interviewer. Each LD form allows for describing six drinking phases. Use a second LD form (visit code "n") if needed to describe additional drinking phases. If this is the second LD form, skip sections B and C and start with item 20.

The interview takes approximately 20 minutes to complete. It is best given after a reasonable degree of rapport has been established, whereby the patient will feel more at ease and talk openly. Other considerable probing and cross-referencing of facts is necessary to help in accurate recall. All information should be recorded under the appropriate heading on the LD form.

A. Center, patient, and visit identification

B. Lifetime alcohol consumption

8. Over the course of your lifetime have you ever had at least one drink of alcohol, beer, liquor, wine, or wine coolers, per month during a 12-month time period, or at least three drinks per day for at least three consecutive days (over a regular period of time):



Patient ID:		

C. First phase

Read as written: "Now, I am going to ask you about your drinking pattern during the first year that you began to have at least one drink per month until your drinking behavior was different in a significant way from this time."

9. How old were you when you began regular drinking:

a. Years:

yrs

b. Months:

mos

10. How old were you at the end of first stage:

a. Years:

yrs

b. Months:

mos

11. During the first stage, how many drinks would you have on average per occasion (*drinking day*):

drinks

12. How many days per month would you generally drink at this level:

days

13. What is the most or maximum number of drinks you would have in any one day:

drinks

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

14. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%):

Beer

%

Liquor

%

Wine

%

15. How would you rate your usual style of drinking during an average month (check the appropriate category);

Abstinent (1)
Occasional (less than 15 days) (2)

Weekend mainly
(3)
Binge (at least 3 days heavy drinking)
(4)

Binge (at least 3 days heavy drinking)
Frequent (15 days or more per month)

(4)
5

16. Did any important event or events occur during this period that altered your usual drinking habits:

Yes No (1) (2) 18.

17. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

Negative Positive Neutral Marital/family . . (2) 3) Work b. 2) 1) 3) School (c. 1) 2) 3) Medical (1) 2) 3) Residence (e. 1) 2) 3) f. Legal/jail 1) 2) Financial g. 1) 2) h. Peer group 1) 2) Drug abuse (i. 1) 2) 3) Treatment (j. 1) 2) 3) k. Death 1) 2) 3) Emotional (

18. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%):

Alone

With others

%

Patient ID:		

During what time of the day would you do most
of your drinking? Could you give me the
percentage of time during the evening, afternoon
and morning (record the relative percentages of
morning, afternoon and evening; this section
should add up to 100%; if not drinking,
percentages should all be "000"):

Morning	 %	
Afternoon	 %	
Evening	 0/	

D. Subsequent phase

20. Read as written: "We have just discussed your drinking habits at the point when you first began to drink regularly. Now I want you to think to when your drinking behavior was different in a significant way from this time. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



- 21. How old were you at the beginning of this phase:
 - a. Years: yrs

 b. Months: mos
- **22.** How old were you at the end of this phase:
 - a. Years: ______yrs
 - **b**. Months:
- **23.** During this phase, how many drinks would you have on average per occasion (*drinking day*):

drinks

24. How many days per month would you generally drink at this level *(write "m" if not drinking)*:

days

25. What is the most or maximum number of drinks you would have in any one day:

#	drinks	

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

26. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

Beer	 ⁰ / ₀	
Liquor	 %	
Wine	 %	

27. How would you rate your usual style of drinking during an average month *(check the appropriate category)*:

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	Ì	5)

28. Did any important event or events occur during this period that altered your usual drinking habits:



29. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

0)) 00		sitive	Neg	ative	Ne	utral
a.	Marital/family (1)	(2)	(3)
b.	Work (1)	(2)	(3)
c.	School (1)	(2)	(3)
d.	Medical (1)	(2)	(3)
e.	Residence (1)	(2)	(3)
f.	Legal/jail (1)	(2)	(3)
g.	Financial (1)	(2)	(3)
h.	Peer group (1)	(2)	(3)
i.	Drug abuse (1)	(2)	(3)
j.	Treatment (1)	(2)	(3)
k.	Death (1)	(2)	(3)
l.	Emotional (1)	(2)	(3)

Patient ID:		

				Taticit ID.	. — —
30.	What percentage of time woul and what percentage of the tim other person (record the relati "Alone" and "With others"; t. add up to 100%; if not drinkin should be "000"):	ne with at least one we percentages of his section should	35.	During this phase, how many drinks have on average per occasion (drinking)	
	Alone _		36.	How many days per month would yo drink at this level (write "m" if not do	
	With others				# days
31.	During what time of the day w		37.	What is the most or maximum number you would have in any one day:	er of drinks
	of your drinking? Could you go percentage of time during the				# drinks
	and morning (record the relati morning, afternoon and evening should add up to 100%; if not percentages should all be "00	ive percentages of ng; this section drinking,		(Note: This is the maximum number to patient actually would drink, not an elemental capacity.)	
	Morning _		20	Whatten of harmon a mould no ma	
	Afternoon	% ————————————————————————————————————	38.	What type of beverage would you use consume in an average month (record percentages of beer, liquor or wine; a should add up to 100%; if not drinkin percentages should all be "000"):	d the relative this section
	_	%		Beer	
E. Ne	xt subsequent phase				%
32.	Read as written: "We have judrinking habits when you first			Liquor	%
	regularly and at a subsequent pyou to think to when your drindifferent in a significant way f	king behavior was		Wine	%
	phase. This could be the next perhaps 2 or 5 years later. Car events in your life that change	6 months or n you think of any d and may have	39.	How would you rate your usual style during an average month (check the a category);	
	altered your drinking habits":	Yes No (1) (2) 81.		Abstinent Occasional (less than 15 days) Weekend mainly Binge (at least 3 days heavy drinking	(1 (2 (3 (3 (4 (4 (4 (4 (4 (4 (4 (4
33.	How old were you at the begin	nning of the phase:		Frequent (15 days or more per month) (½
	a. Years:	yrs			
	b . Months:	mos			

34. How old were you at the end of this phase:

a. Years:

b. Months:

yrs

mos

Patient ID:		

40. Did any important event or events occur during this period that altered your usual drinking habits:

Y	es '	N	lo
(1)	(2)
	42]◆	_

41. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Nega	itive	Neu	ıtral
a.	Marital/family	. (1)	(2)	(3)
b.	Work	(1)	(2)	(3)
c.	School	(1)	(2)	(3)
d.	Medical	(1)	(2)	(3)
e.	Residence	(1)	(2)	(3)
f.	Legal/jail	(1)	(2)	(3)
g.	Financial	(1)	(2)	(3)
h.	Peer group	(1)	(2)	(3)
i.	Drug abuse	(1)	(2)	(3)
j.	Treatment	(1)	(2)	(3)
k.	Death	(1)	(2)	(3)
l.	Emotional	(1)	(2)	(3)

42. What percentage of time would you drink alone, and what percentage of the time with at least one other person (record the relative percentages of "Alone" and "With others"; this section should add up to 100%; if not drinking, percentages should be "000"):

Alone		
	9/0	
With others		
	%	

43. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 %	
Afternoon	 %	
Evening	 %	

- F. Next subsequent phase
- 44. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



45. How old were you at the beginning of the phase:

a.	Years:	
		yrs

- **b**. Months:
- **46.** How old were you at the end of this phase:

a.	Years:	
		yrs
b.	Months:	
		mos

47. During this phase, how many drinks would you have on average per occasion *(drinking day)*:

drinks

48. How many days per month would you generally drink at this level (write "m" if not drinking):

days

49. What is the most or maximum number of drinks you would have in any one day:

(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

Patient ID:		

50.	What type of beverage would you usually
	consume in an average month (record the relative
	percentages of beer, liquor or wine; this section
	should add up to 100%; if not drinking,
	percentages should all be "000"):

Beer	 %	
Liquor	 <u>%</u>	
Wine	 <u>%</u>	

51. How would you rate your usual style of drinking during an average month *(check the appropriate category)*;

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	(5)

52. Did any important event or events occur during this period that altered your usual drinking habits:



53. What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

		Posit	ive	Neg	ative	Ne	utral
a.	Marital/family	. (1)	(2)	(3)
b.	Work	. (1)	(2)	(3)
c.	School	. (1)	(2)	(3)
d.	Medical	. (1)	(2)	(3)
e.	Residence	. (1)	(2)	(3)
f.	Legal/jail	. (1)	(2)	(3)
g.	Financial	. (1)	(2)	(3)
h.	Peer group	. (1)	(2)	(3)
i.	Drug abuse	. (1)	(2)	(3)
j.	Treatment	. (1)	(2)	(3)
k.	Death	. (1)	(2)	(3)
l.	Emotional	. (1)	(2)	(3)

54.	What percentage of time would you drink alone,
	and what percentage of the time with at least one
	other person (record the relative percentages of
	"Alone" and "With others"; this section should
	add up to 100%; if not drinking, percentages
	should be "000"):

Alone	 %	
With others	 <u>%</u>	

55. During what time of the day would you do most of your drinking? Could you give me the percentage of time during the evening, afternoon and morning (record the relative percentages of morning, afternoon and evening; this section should add up to 100%; if not drinking, percentages should all be "000"):

Morning	 <u></u>
Afternoon	 <u>′</u>
Evening	

G. Next subsequent phase

56. Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":



57. How old were you at the beginning of the phase:

a.	Years:	,
		yrs
b.	Months:	
		mos

58. How old were you at the end of this phase:

a.	Years:	
		yrs
b.	Months:	
		mos

Patient ID:		

59.60.	During this phase, how many drinks would you have on average per occasion (drinking day): # drinks How many days per month would you generally	65.	What was your perception of you say that it had a positive (undesirable), or neutral (no) (for each event that influence drinking pattern, check "1" "2" for negative effect or "3 effect):	(desirable), negative effect on your life ed the patient's for positive effect or
	drink at this level (write "m" if not drinking):			
			Positiv	
	# days		a. Marital/family (b. Work (1) (2) (3)
	4450		c . School ($ \begin{array}{cccccccccccccccccccccccccccccccccccc$
61.	What is the most or maximum number of drinks		d . Medical ($ \begin{array}{cccccccccccccccccccccccccccccccccccc$
	you would have in any one day:		e. Residence ($ \begin{array}{cccccccccccccccccccccccccccccccccccc$
			f. Legal/jail ($ \begin{array}{cccccccccccccccccccccccccccccccccccc$
	# drinks		g. Financial (1) (2) (3)
	(Note: This is the maximum number that the		h . Peer group (1) (2) (3)
	patient actually would drink, not an estimate of		i. Drug abuse (1) (2) (3)
	his/her potential capacity.)		j. Treatment (k. Death (1) (2) (3)
			l. Emotional ($ \begin{array}{cccccccccccccccccccccccccccccccccccc$
	consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"): Beer	66.	What percentage of time wor and what percentage of the ti- other person (record the rela "Alone" and "With others"; add up to 100%; if not drinks should be "000"):	ime with at least one tive percentages of this section should
	Liquor			%
	%		With others	
	Wine		with others	<u>%</u>
63.	How would you rate your usual style of drinking during an average month (check the appropriate category);	67.	During what time of the day of your drinking? Could you percentage of time during the and morning (record the relamorning, afternoon and even should add up to 100%; if no	a give me the e evening, afternoon ative percentages of thing; this section
	Abstinent (1) Occasional (less than 15 days) (2)		percentages should all be "0	
	Occasional (less than 15 days) (2) Weekend mainly (3)		percentages should all oc	· · · · · ·
	Binge (at least 3 days heavy drinking) (4)		Morning	
	Frequent (15 days or more per month) (5)			%
64.	Did any important event or events occur during this period that altered your usual drinking habits:		Afternoon	
	Yes No		Evening	
	(1) (2)		Č	%
	<u>66.</u> ◀			

Patient ID:		

H. Next subsequent phase

Read as written: "We have just discussed your drinking habits when you first began to drink regularly and at subsequent phases. Now I want you to think to when your drinking behavior was different in a significant way from the previous phase. This could be the next 6 months or perhaps 2 or 5 years later. Can you think of any events in your life that changed and may have altered your drinking habits":

Y	es	N	lo
(1)	(2)
	81]◆	

69.	How	old	were	vou	at	the	begin	ning	of	the	phase	9
U).	110 00	Olu	WCIC	you	иı	uic	UCSII.	யயத	O1	uic	pmas	_

l.	Years:	

			<i>J</i> 10
b.	Months:	_	
		_	mos

70. How old were you at the end of this phase:

a.	Years:	
		yrs

b. Months:

71.

		mos
During this phase	how many drinks	would you

have on average per occasion (drinking day):

72. How many days per month would you generally drink at this level (write "m" if not drinking):

# days	

73. What is the most or maximum number of drinks you would have in any one day:



(Note: This is the maximum number that the patient actually would drink, not an estimate of his/her potential capacity.)

74. What type of beverage would you usually consume in an average month (record the relative percentages of beer, liquor or wine; this section should add up to 100%; if not drinking, percentages should all be "000"):

Beer	 %	
Liquor	 %	
Wine	 <u>%</u> -	

75. How would you rate your usual style of drinking during an average month (check the appropriate category);

Abstinent	(1)
Occasional (less than 15 days)	(2)
Weekend mainly	(3)
Binge (at least 3 days heavy drinking)	(4)
Frequent (15 days or more per month)	(5)

Did any important event or events occur during this period that altered your usual drinking habits:



What was your perception of this event? Would you say that it had a positive (desirable), negative (undesirable), or neutral (no) effect on your life (for each event that influenced the patient's drinking pattern, check "1" for positive effect or "2" for negative effect or "3" for neutral or no effect):

	Pos	itive	Neg	gative	Ne	utral
a.	Marital/family (1)	(2)	(3)
b.	Work (1)	(2)	(3)
c.	School (1)	(2)	(3)
d.	Medical (1)	(2)	(3)
e.	Residence (1)	(2)	(3)
f.	Legal/jail (1)	(2)	(3)
g.	Financial (1)	(2)	(3)
h.	Peer group (1)	(2)	(3)
i.	Drug abuse (1)	(2)	(3)
j.	Treatment (1)	(2)	(3)
k.	Death (1)	(2)	(3)
l.	Emotional (1)	Ì	2)	(3)

Patient ID:		

78.	and what perce other person (re "Alone" and "	ntage of the time ecord the relative With others"; the first of the thinking if not drinking the thinking the	d you drink alone, e with at least one we percentages of his section should g, percentages
	Alone	_	
	With others	_	
79.	of your drinkin percentage of t and morning (r morning, aftern should add up	g? Could you gime during the e	evening, afternoon we percentages of eg; this section drinking,
	Morning	_	
	Afternoon	_	
	Evening	_	
I. Nui	nber of phases		
80.	Are there any a	dditional subse	quent phases: Yes No (* 1) (2)
		ete a second LD and C on secor	
J. Adn	ninistrative info	ormation	
81.	Clinical Coord	inator PIN: _	
82.	Clinical Coord	inator signature	
83.	Date form revie		
	day	mon	year

FLINT

LR - Laboratory Results - Tests Done at Screening and Followup Visits

Purpose: To record archival and current laboratory test results for tests done during both screening and followup. **When**: Visits s, f12, f24, f36, f48, f60, f72, and f96.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. Attach copies of the laboratory reports to this form. If is checked for any item, then the form should not be keyed.

A. Center, patient, and visit identification	12. Mean corpuscular volume (MCV):
1. Center ID:	
2. Patient ID:	13. White blood cell count (WBC):
3. Patient code:	$10^3 \text{ cells/} \mu\text{L} \text{ or } 10^9 \text{ cells/} \text{L}$
4. Date of visit:	14. Platelet count:
day mon year 5. Visit code:	If platelets < 100,000 cells/mm ³ (mm ³ = μ L) at screening, patient is ineligible.
6. Form & revision:	C. Chemistries Required at visits s, f24, f48, f72, and f96.
7. Study: FLINT <u>7</u>	15. Is metabolic panel required at this visit: $ \begin{pmatrix} Yes \\ 1 \end{pmatrix} $ $ \begin{pmatrix} No \\ 2 \end{pmatrix} $
B. Hematology Required at visits s, f24, f48, f72, and f96.	28.
8. Is hematology testing required at this visit:	16. Date of blood draw for chemistries:
Yes (Yes (No 2) 15. —) 9. Date of blood draw for complete blood	day mon year Date must be within the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's FLINT visit time window guide).
count:	17. Sodium:
day mon year Date must be within the required time window; within 90 days of liver biopsy or in the time window	18. Potassium:
for the followup visit (check the patient's FLINT visit time window guide).	19. Chloride:
10. Hemoglobin:	20. Bicarbonate:
11. Hematocrit:	21. Calcium:

22.	Phosphate:	mg/dL	E. Hem
23.	Blood urea nitrogen (BUN)):	32. Is I
24.	Creatinine (if serum creating patient is ineligible):	nine $\geq 2.0 \text{ mg/dL}$,	
	-	mg/dL	33. Da
25.	Uric acid:	mg/dL	Da wii
26.	Albumin (if albumin < 3.2 ineligible):	g/dL, patient is	wii FL
			34. Hb of i
27.	Total protein:		
D. P	rothrombin time and INR		
	Required at visits s and f72	2.	F. Liver
28.	Are the prothrombin time a required at this visit:	and INR	35. Da
	required at this visit.	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	33. Da
		32.	Da
29.	Date of blood draw for propand INR:	thrombin time	wit for vis
		mon year	36. Bil
	Date must be in the require 90 days of liver biopsy or	ed time window; within in the time window for	
	the followup visit (check th time window guide).	e patient's FLINT visit	37. Bil (if ine
30.	Prothrombin time (PT):		

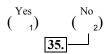
31. International normalized ratio (INR)

(if INR > 1.3, patient is ineligible):

oglobin A1c

equired at visits s, f24, f48, f72, and f96.

HbA1c required at this visit:



te of blood draw for HbA1c:

day	mon	vear

te must be within the required time window; thin 60 days of randomization or in the time ndow for the follow-up visit (check the patient's INT visit time window guide).

Alc (if HbA1c is $\geq 9.5\%$ within 60 days randomization, patient is ineligible):



r panel

quired at all visits.

te of blood draw for liver panel:

		_ _
day	mon	year

te must be within the required time window; thin 90 days of liver biopsy or in the time window the follow-up visit (check the patient's FLINT sit time window guide).

lirubin (total):

lirubin (conjugated or direct) direct bilirubin > 1.3 mg/dL, patient is eligible):

38. Aspartate aminotransferase (AST)

U/L

a. Upper limit of normal:

39. Alanine aminotransferase (ALT) (if ALT > 300 U/L at screening, patient is ineligible)	H. Fasting glucose and insulin tolerance test	S
	Fasting glucose and insu visits; the 2 hour OGTT is f72 for nondiabetics.	ain are requirea at all required at visits s and
a. Upper limit of normal:	The 2 hour oral glucose performed in the morning night fasting. Blood samp	g after a 12-hour over-
40. Alkaline phosphatase U/	measurements of serum baseline and 2 hours (1 administration of a flavor	glucose and insulin a 20 minutes) after ora ed glucose solution in a
a. Upper limit of normal: U/	dose of 2 g/kg (75 g maxin 44. Was participant fasting for	
41. Gamma glutamyl transferase (GGT):	hours:	
		$\binom{\text{Yes}}{1}$ $\binom{\binom{\text{No}}{*}}{2}$
	*Patient must be fasting;	12 hour fasting is nre-
G. Fasting lipid profile Required at all visits	ferred. Fasting glucose of tained at visit s.	
Fasting is defined as nothing by mout. water for greater than or equal to 12 hou to blood draw.		sting glucose
42. Was participant fasting for at least 8 hours prior to blood draw:		mon year
Yes (1) *12 hour fasting is preferred, but will acc fasting lipid values.	$\binom{N_0}{*_2}$ Date must be within 90 do the time window for the form	ays of liver biopsy or in ollowup visit (check the
43. Date of blood draw for fasting lipid	46. Result of baseline fasting levels	glucose/insulin
profile:	a. Serum glucose:	
		mg/dL
day mon Date must be within the required time within 90 days of liver biopsy or in the time	window	$-\!$
for the followup visit (check the patient' visit time window guide).	<i>FLINT</i> 47. Is glucose tolerance test (0)	OGTT) required
a. Triglycerides:	at this visit (the 2 hour OC s and f72 for nondiabetics	GTT is required at visits
mg dE	Yes	(1)
b. Total cholesterol: mg/	dL No	(2)
c. HDL cholesterol level:	No, patient is diabetic	49. 3 49. 3
d. LDL cholesterol level*:	48. OGTT results at 2 hours	
*Enter ''GT'' if LDL cannot be calculate high triglycerides.		mg/dL

 $\overline{\mu U/mL}$

b. Serum insulin:

I. Pregnancy test

Required at all study visits, if applicable.

49. Is pregnancy test applicable:

(Y	res 1	(No 2)
		52.

50. Date of urine collection (or blood draw):

_		_
day	mon	year

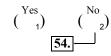
Date must be the same day as date of visit.

51. Pregnancy test result (if pregnancy test is positive at screening visit, patient is ineligible):

Positive	(1)
Negative	(2)

J. Eligibility check

52. Is this the screening visit:



53. Was the patient found to be ineligible based on platelet count (item 14), creatinine (item 24), albumin (item 26), INR (item 31), HbA1c (item 34), direct bilirubin (item 37), ALT (item 39) or pregnancy test (item 51) or based on missing tests:



K. Administrative information

- **54.** Study Physician PIN:
- **55.** Study Physician signature:
- **56.** Clinical Coordinator PIN: ____ ___
- **57.** Clinical Coordinator signature:
- **58.** Date form reviewed:

mon

year

LS - Laboratory Results -Tests Done only During Screening

Purpose: To record archival and current results of laboratory tests done only during screening.

When: Visit s.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have questions about conversion or how to record a value. Staple the lab report to the back of this form. If your lab reports values electronically, print a copy of the results and staple the report to the back of this form. If is checked for any item, you do not need to complete the rest of the form and the form should not be keyed.

A. Center, patient, and visit identification		B. Screening etiologic tests		
1. Center ID:		8. Date of blood draw for serological assays to exclude viral causes of chronic liver		
2. Patient ID:		disease:		
3. Patient code:	———	day mon year Repeat if date is greater than 1 year prior to screening.		
4. Date of visit:		If the patient is judged by Study Physician to have a high-risk lifestyle, repeat if date is greater than		
day	mon year	3 months prior to screening.		
5. Visit code:	_S	a. Hepatitis B surface antigen (HBsAg): Positive		
6. Form & revision:	_ls1_	Negative (2)		
7. Study:	FLINT 7	b. Hepatitis B core total antibody (anti-HBc) (if total anti-HBc is not available, record results from IgG test): Positive		
		Negative (2)		
		Not available $\begin{pmatrix} 2 \\ 3 \end{pmatrix}$		
		c. Hepatitis B surface antibody (anti-HBs):		
		Positive (1)		
		Negative (2)		
		Not available $\begin{pmatrix} & & & \\ & & & \end{pmatrix}$		
		d. Hepatitis C virus RNA (HCV RNA):		
		Positive ()		
		Negative (2)		
		Not available $\begin{pmatrix} 2 \\ 3 \end{pmatrix}$		

e. Hepatitis C antibody (anti-HCV)
(indicate result as negative if EIA is
positive but RIBA is negative or if RIBA
is indeterminate but HCV RNA is negative):
Positive

(Ling)—

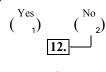
C. Iron

Negative

9. Date of blood draw for iron overload screening:

day	 mon	year
Repeat if date is g screening.	reater than 1 y	vear prior to
a. Iron:		$\mu g/dL$
b. Total iron binding	g capacity:	µg/dL
c. Ferritin:		
	n	g/mL

10. Is hepatic iron index available:



11. Hepatic iron index:

•	
μMo1/g/year	_

D. HFE gene analysis

12. Does the patient have an abnormality in an iron overload screening test, a family history of iron overload or hemochromatosis, or histological iron of greater than 3+:



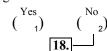
13. Date of blood draw for HFE gene analysis:

=		_
day	mon	year

14. Type of abnormality (WT = wild type; check only one):

None	(0)
C282Y/H63D heterozygote mutation	(1)
C282Y/C282Y homozygote mutation	(2)
C282Y/WT heterozygote mutation	(3)
H63D/WT heterozygote mutation	(4)
H63D/H63D homozygote mutation	(ر ا

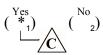
- E. Ceruloplasmin
- **15.** Is patient 40 years old or younger:



16. Date of blood draw for ceruloplasmin: (required only if patient is 40 years old or younger):

day mon year Repeat if date is greater than 5 years prior to screening.

- 17. Ceruloplasmin ______ _____
 - a. Upper limit of normal: _____ mg/dL
 - **b.** Lower limit of normal: _____ _ _ _ _ _ _ ___
 - **c.** Is ceruloplasmin < LLN:



*Check liver biopsy histology findings for Wilson's disease.

_			
н.	Alpha-	1 anti	trvpsin

18.	Date of blood draw for alpha-
	antitrypsin (A1AT):

day	mon	year
Repeat if date is great	er than 5 ye	ears prior to

screening.

19. Alpha-1 antitrypsin (A1AT)	
1 21 \	ma/dI

b. Lower limit of normal:
$$\underline{\qquad}_{mg/dL}$$

20. A1AT phenotype:

Yes	(1)
No	(2)
Unknown	(3)
h Pi 77 homozygote:		

b. 11 ZZ nomozygote.		
Yes	(1
No	(

21. A1AT deficiency as a contributor to liver disease (physician judgment):



G. Autoantibody studies

22. Date of blood draw for antinuclear antibody tests:

_		_
day	mon	year

Repeat if date is greater than 5 years prior to screening.

23.	Antinuclear	antibody	(ANA)	١.

	• • • • • • • • • • • • • • • • • • • •	
Positive		(*1)
Negative		(2)
		24.

a. Titer (record only the denomin	ator).
-----------------------------------	--------

b. Units:	•	

24. Date of blood draw for antismooth muscle antibody tests:

screening.

day		mon	_		year	
Repeat if date	is greater	than	5	vears	prior	to

25. Antismooth muscle antibody (ASMA):

Positive	(*1)
Negative	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
	26.

9	Titer	(record	only	the	lonom	inator	١.
a.	Hitel	trecora	oniv	ine a	enom	maiori	

1/	 	

26. Date of blood draw for antimitochondrial antibody tests:

•		
day	mon	year
Repeat if date is great screening.	er than 5 yea	ers prior to

27. Antimitochondrial antibody (AMA):

Positive	(*1)
Negative	(2)
	28.
*If positive AMA	value, complete either a or h

depending on laboratory results:

a. Titer (record only the denominator):

1/	 	
	•	

^{*}If positive ANA value, complete either a or b depending on laboratory results:

^{*}If positive ASMA value, complete either a or b depending on laboratory results:

T	•		.1			. 4	4.		•	- 4 *
ł	1.	А	a	ımı	nıs	Tr:	ITIVE	ını	orm	ation

28. Study Physician PIN:

29. Study Physician signature:

30. Clinical Coordinator PIN:

31. Clinical Coordinator signature:

32. Date form reviewed:

mon

year

LT - Liver Tissue Banking

Purpose: To document collection of extra liver tissue and procedures for liver tissue banking.

When: Visits s and f72 when more than 2 cm of liver tissue are obtained during a biopsy. This form is expected when the Liver Biopsy Materials Documentation (SD) form says liver tissue was obtained for banking.

By whom: Clinical Coordinator, in consultation with study physician.

Instructions: Liver biopsy tissue should be obtained by a needle core biopsy (as opposed to a wedge biopsy) using a 16 gauge or greater needle. Whenever more than 2 cm of tissue are obtained during biopsy, place a 1-2 mm segment of liver tissue into a labeled 2.0 mL polypropylene cryovial pre-filled with approximately 1 mL of RNA*later*® Solution. Liver tissue should be placed in RNA*later*® Solution within one minute and no more than 5 minutes after biopsy. Note: If the sample is not placed in RNA*later*® Solution within 5 minutes, discard the cryovial. Refrigerate the cryovial at 4° C overnight to allow thorough penetration of the liver tissue and then transfer to -70° C freezer for storage. Batch ship cryovials monthly on dry ice to the NIDDK Biosample Repository located at Fisher BioServices.

A. Center, patient and visi	t identification	11. Was liver tissue refrigerated at 4° C overnight, then transferred to freezer for
1. Center ID:		storage.
2. Patient ID:		$ (Yes \atop 1) \qquad (No \atop 2) $
3. Patient code:		a. If no, describe conditions of local storage:
4. Date form initiated:		
day	mon year	
5. Visit code (s or f72):		C. Cryovial label
6. Form & revision:	<u>l t 2</u>	12. Attach duplicate cryovial label (make sure you attach the duplicate of the label attached to the cryovial holding the liver tissue from this biopsy):
7. Study:	FLINT_7_	cryoviai notaing the tiver tissue from this biopsy).
procedures8. Date of biopsy:		
	mon year	
9. Was the liver tissue obtaneedle core biopsy (as biopsy):	opposed to a wedge	
	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{2}$	D. Administrative information
10. Was liver tissue placed Solution preferably wit		13. Clinical Coordinator PIN:
no more than 5 minutes	s after biopsy:	14. Clinical Coordinator signature:
	$\binom{\text{Yes}}{1}$ $\binom{\text{No}}{*}_{2}$	15. Date form reviewed:
* Discard liver tissue	13.	13. Date form reviewed.
		day mon year

MR - MRI Consent and Report Form

Purpose: To document the collection and transmittal of MRI data.

When: Visit s and f72.

By whom: Study Radiologist/Study Physician and Clinical Coordinator.

Instructions: Complete this form based on the consent documents signed by the patient. Patient may still participate in FLINT trial without an MRI. Please consult FLINT SOP VI for additional procedures.

Before MRI examination review the following basic information with subjects: 1) Subjects should fast for four or more hours if possible before the MRI examination. 2) Necessary medications are allowed with small amounts of water. 3) Rehearse breathing instructions with subject. Subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and to reduce discomfort associated with breath-holding. 4) Explain the necessity of remaining still during the MRI examination.

On day of MRI examination confirm the following information with subjects: 1) Subject identity. 2) MRI consent is signed and a copy of consent kept on site. 3) No MRI contraindications. 4) Emptied bladder prior to scanning. 5) Subject has been weighed, and been asked height. 6) MRI-compatible clothing (no metal or metallic/shiny clothing). 7) Breathing instructions rehearsed and understood (subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and reduce discomfort associated with breath-holding).

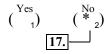
Pre-MRI preparation: 1) Subjects to be positioned supine. 2) Ensure subject comfortable on scanner table. 3) For 3T MRIs, place dielectric pad over liver. 4) Place phased-array coil (over dielectric pad, for 3T scanners) centered over the liver; ensure good connection to scanner.

A. Center, patient and visit identification

- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- 4. Date form completed:

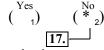
_		_
day	mon	year

- **5.** Visit code: ____ ___
- **7.** Study: FLINT _7_
- **8.** Is FLINT MRI protocol currently in use at your center:



B. Consent

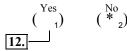
9. Has the patient signed the FLINT MRI consent:



* An MRI should not be performed unless consent is obtained.

C. MRI results and information

10. Was an MRI performed:



17 -

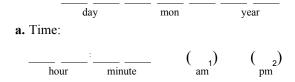
- * Complete item 11, then skip to item 17.
- **11.** Reason MRI not performed *(check all that apply)*
 - a. Patient was not fasting: (
 - **b.** Patient suffers from extreme claustrophobia:
 - c. Patients weight or girth exceeds MRI scanner capabilities:
 - **d.** Other (specify):

Technician name:	

print name

13. Date and time of MRI:

12.



MV - Missed or Incomplete Visit

Purpose: Record the reason(s) for a missed or incomplete visit.

When: At the close of a visit window for any missed follow-up visit or for any follow-up visit with specific forms not completed.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in

missing forms) within the time window for the visit.

A. Center, patient, and visit identification	1	10. Steps taken to avoid missing the visit <i>(check all that apply)</i>		
1. Center ID:		a. Telephoned patient:	(1)
		b. Mailed reminder card:	(1)
2. Patient ID:		c. Other (specify):	(1)
3. Patient code:		specify		
4. Date form completed:		14]—	J
day mon	year	D. Missed form information		
5. Visit code: <u>f</u>		11. Check form(s) not completed (check all that apply)		
6. Form & revision: m	<u>v</u> 1	a. Blood Processing for Plasma and Serum (BP):	(1)
7. Study: FI	INT_7_	b. Follow-up Medical History (HI):	(1)
B. Reason for completion of this form		c. Laboratory Results - Tests Done During Screening and Followup (LR):	(1)
		d. Liver Tissue Banking (LT):	(1)
8. Was the entire visit missed:	No	e. Physical Examination (PE):	(1)
$\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}$	(2)	f. Focused Physical Examination (PF):	(1)
	11.	g. SF-36v2 Health Survey (QF):	(1)
C. Missed visit information		h. Study Drug Dispensing and Return (RD):	(1)
9. Reason for missed visit (check all that		i. Liver Biopsy Materials Documentation	(`
a. Patient was ill:	(1)	(SD):	(1)
b. Patient was temporarily away from area:	(1)	j. MRI Consent and Documentation (MR):	(1)
c. Patient refused to return:	(1)	k. Other (specify):	(1)
d. Patient has permanently moved from the area:	m (₁)	specify		
e. Unable to contact patient:	(1)			
f. Other (specify):	(1)			
specify				

12.	Reason form(s) not completed (check all that apply)		
	a. Patient was ill:	(1)
	b. Patient refused procedure:	(1)
	c. Procedure forgotten:	(1)
	d. Other (specify):	(1)
	specify		
13.	Attempts made to complete form(s) (check all that apply)		
	a. Attempted to reschedule procedure:	(1)
	b. Attempted to collect interview data by phone from patient:	(1)
	c. Attempted to gain patient cooperation:	(1)
	d. Other (specify):	(1)
	specify		
E. A	dministrative information		
14.	Clinical Coordinator PIN:		
15.	Clinical Coordinator signature:		
16.	Date form reviewed:		
	day mon	year	

- **14.** Dates images sent to MRI Reading Center
 - a. By CD/DVD:

day mon year

b. By secure in-server connection (enter "m" if not available):

day mon year

- D. Administrative information
- **15.** Study Radiologist or Study Physician PIN:

16. Study Radiologist or Study Physician signature:

17. Clinical Coordinator PIN: ____ ___

18. Clinical Coordinator signature:

19. Date form reviewed:

day mon year

PE - Physical Examination

Purpose: Record detailed physical exam findings.

When: Visits s, f24, f48, f72, and f96.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist, and hip measurements are found in the FLINT SOP, Part I. In brief: Height, weight, waist, and hips all should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

A. Center, patient, and visit identification	9. Weight (shoes off)
1. Center ID:	a. Weight, 1st measurement:
2. Patient ID:	b. Weight, 2nd measurement:
3. Patient code:	
4. Visit date:	Pounds (1)
day mon year	Kilograms (₂)
5. Visit code:	10. Waist (standing, at midpoint between highest point of iliac crest and lowest part of costal margin; repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other)
6. Form & revision:	a. Circumference, 1st measurement:
7. Study: FLINT7	<u></u>
B. Measurements	waist circumference b. Circumference, 2nd measurement:
8. Height (shoes off)	waist circumference
a. 1st measurement:	c. Units:
•	Inches (1)
b. 2nd measurement:	Centimeters (2)
c. Units:	11. Hip (standing, at fullest part of the hips; repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other)
Centimeters (a. Circumference, 1st measurement:
	•
	hip circumference
	b. Circumference, 2nd measurement:
	hip circumference
	c. Units:
	Inches (1)
	Centimeters (₂)

12. Temperature (oral)		19. Focused liver signs <i>(check all t</i>	hat apply)
a. Degrees:	•	a. None:	(
a. Degrees.	· —— ——	b. Jaundice:	(
b. Scale:		c. Palmar erythema:	(
Fahrenheit	$\begin{pmatrix} & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ \end{pmatrix}$	d. Contractures:	(
Centigrade	(2)	e. Pedal edema:	(
13. Blood pressure		f. Spider angiomata:	(
a Systalia		g. Asterixis:	(
a. Systolic:	mmHg	h. Hepatic encephalopathy:	(
1 D' 4 I'		i. Wasting:	(
b. Diastolic:	mmHg	j. Fetor:	(
14. Resting radial pulse:		k. Pruritus:	(
14. Resulig radial pulse.	beats/minute	1. Other, (specify):	(
15. Respiratory rate:			
Tet Iteophius j iuw.	breaths/minute	specify	
C. Examination findings		D. Administrative information	
16. Chest and lungs:		20. Study Physician PIN:	
Normal	(1		
Abnormal	17. (₂)	21. Study Physician signature:	
specify abnormal	lity	22. Clinical Coordinator PIN:	
17. Heart:			
Normal	(1)	23. Clinical Coordinator signature:	
	18.		
Abnormal	(2)	24 D 4 C	
specify abnormal	lity	24. Date form reviewed:	_
specify abilotina.	nty	day mon	year
18. Abdomen abnormalities present <i>(check all that apply):</i>	t		
a. None:	(1)		
b. Ascites:	(1)		
c. Obese:	(1)		
d. Splenomegaly:	(1)		
e. Hepatomegaly:	(1)		
If Yes, span at right midclavi	icular line:		

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.

When: Visits f12, f36, and f60.

Administered by: Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height and weight are found in the FLINT SOP Part I. In brief: height and weight should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures.

A. Center, patient, and visit	t identification	10. Temperature (oral)			
1. Center ID:		a. Degrees:	<u> </u>		
2. Patient ID:		b. Scale:			
		Fahrenheit:	(1)		
3. Patient code:		Centigrade:	(₂)		
4. Visit date:		11. Blood pressure			
	mon year	a. Systolic:	 mmHg		
5. Visit code:	_f	b. Diastolic:			
6. Form & revision:	_p_f_1_	12 Desting radial nulsar	mmHg		
	•	12. Resting radial pulse:	beats/minute		
7. Study:	FLINT_7	13. Respiratory rate:	breaths/minute		
B. Measurements			breatis/illiliae		
		C. Administrative information			
8. Height (shoes off)		44 611 1 1 6 11 1 15			
a. 1st measurement:		14. Clinical Coordinator ID:			
b. 2nd measurement:	· · · · · ·	15. Clinical Coordinator signature:			
c. Units:					
Inches	(1)	16. Date form reviewed:			
Centimeters	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$				
9. Weight (shoes off)	. 2	day mon	year		
a. 1st measurement:					
	•				
b. 2nd measurement:					
c. Units:					
Pounds	()				
Kilograms	(1)				

QF - SF-36v2 Health Survey

Purpose: To obtain the patient's views of his/her health in the FLINT trial. **When**: At screening visit s and follow-up visits f24, f48, f72, and f96.

Administered by: Self-administered, but Clinical Coordinator must be available at visit to answer questions and to review completed forms.

Respondent: Patient.

Instructions: The Clinical Coordinator should complete section A and attach a MACO label to each of pages 2-7 before giving the questionnaire to the patient for completion. The Clinical Coordinator should review the completed questionnaire for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-7 and the Clinical Coordinator should complete section B.

A. Center, patient, and visit identification					B. Administrative information (To be completed by clinical center staff after survey)				
1.	Center ID:			is completed.)					
2.	Patient ID:		·	8.	Clinical Coor	dinator			
3.	Patient code:				a. PIN:b. Signatur	re:			
4.	Date of visit (date p	atient complete	d the form):						
		mon	year	9.	Date form rev	iewed:			
5.	Visit code:				day	mon	year		
6.	Form & revision:	<u>q</u>	<u>f</u> 1						
7.	Study.		FLINT 7						

Affix label here						
Patient ID:						
Patient code:						
Visit code:						

SF-36v2 Health Survey

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

(Items 1-9 are reserved for clinical center use.)

10. In general, would you say your health is:

	Circl	le one
Excellent		1
Very good		2
Good		3
Fair		4
Poor		5

11. Compared to one year ago, how would you rate your health in general now?

	Circ	ie one
Much better now than one year ago		1
Somewhat better now than one year ago		2
About the same as one year ago		3
Somewhat worse now than one year ago		4
Much worse now than one year ago		5

Affix lal	bel here
Patient ID:	
Patient code:	
Visit code:	

12. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Circle one		
	Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports:	1	2	3
b.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:	1	2	3
c.	Lifting or carrying groceries:	1	2	3
d.	Climbing several flights of stairs:	1	2	3
e.	Climbing one flight of stairs:	1	2	3
f.	Bending, kneeling, or stooping:	1	2	3
g.	Walking more than a mile:	1	2	3
h.	Walking several hundred yards:	1	2	3
i.	Walking one hundred yards:	1	2	3
j.	Bathing or dressing yourself:	1	2	3

Affix label here				
Patient ID:				
Patient code:				
Visit code:				

13. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical</u> health?

		Circle one				
		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the <u>amount of</u> <u>time</u> you spent on work or other activities:	1	2	3	4	5
b.	Accomplished less than you would like:	1	2	3	4	5
c.	Were limited in the <u>kind</u> of work or other activities:	1	2	3	4	5
d.	Had difficulty performing the work or other activities (for example, it took extra effort):	1	2	3	4	5

14. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

		Circle one				
		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Cut down on the <u>amount of</u> <u>time</u> you spent on work or other activities:	1	2	3	4	5
b.	Accomplished less than you would like:	1	2	3	4	5
c.	Did work or other activities less carefully than usual:	1	2	3	4	5

Affix label here	
Patient ID:	
Patient code:	
Visit code:	:

15. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?

	Circle on
Not at all	
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

16. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

	Circle one
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

17. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

	Circle one
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

Affix label here				
Patient ID:				
Patient code:				
Visit code:				

18. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>:

		Circle one				
		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Did you feel full of life?	1	2	3	4	5
b.	Have you been very nervous?	1	2	3	4	5
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d.	Have you felt calm and peaceful?	1	2	3	4	5
e.	Did you have a lot of energy?	1	2	3	4	5
f.	Have you felt downhearted and depressed?	1	2	3	4	5
g.	Did you feel worn out?	1	2	3	4	5
h.	Have you been happy?	1	2	3	4	5
i.	Did you feel tired?	1	2	3	4	5

19. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

	Circle one	,
All of the time	1	
Most of the time	2	
Some of the time	3	
A little of the time	4	
None of the time	5	

Affix label here	
Patient ID:	į
Patient code:	į
Visit code:	į

20. How TRUE or FALSE is <u>each</u> of the following statements for you:

			. (Circle one		
		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

Today's date:			

Thank you for completing this survey, please return this questionnaire to the coordinator.

RC - Rescreen in FLINT

Purpose: To rescreen a patient who was previously found to be ineligible for FLINT due to a temporary ineligibility. This form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 112-day screening window starts). The original RG form completed for the patient must remain in the data system. New screening labels will be available for printing upon keying this form.

When: Visit code s.

Administered by: Clinical Coordinator.

Respondent: None.

Instructions: Complete this form for a patient who was previously found to be ineligible for FLINT due to a temporary ineligibility and who now wants to rescreen for FLINT. In general, the patient must complete all FLINT screening data collection anew and all previously keyed FLINT screening forms should be deleted from the data system except the RG and possibly the CG form. If needed, update section C (only education and employment history) of the RG form and update the keyed record (you cannot delete the RG form); note that the patient's age will not change since it is based on the date of the RG form. If any changes are made in section C, the review date in section F should be updated. If blood was collected successfully for the Genetics Repository, a new sample does not need to be collected and the previously completed CG form may remain unchanged in the data system. Plasma and serum must be collected anew. If the same liver biopsy is being used to satisfy eligibility now and slides were sent to the DCC, additional slides do not need to be sent.

A. Center, pa	itient, and v	isit identifi	cation	C. Admin	istrative infor	mation	
1. Center ID) :			9. Clinic	al Coordinator	PIN:	
2. Patient ID) :			10. Clinic	eal Coordinator	signature:	
3. Patient co	ode:	-					
4. Date of v	isit:			11. Date 1	form reviewed:		_
_	day	mon	year		day	mon	year
5. Visit code	e:	· -	s				
6. Form & r	evision:	_	<u>r c 1</u>				
7. Study:			FLINT 7				
B. FLINT pa	rticipation						
8. Date in its form:	em 4 of orig	inal FLINT	RG				
_	dav	mon	vear				

Purpose: To record dispensing and return of study drug.

When: Visits rz, f12, f24, f36, f48, f60, and f72. Use visit code "n" if study drug is dispensed or returned at a time other than study visits or if a second form is needed at a visit to document returned study drug.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Instructions: This form documents dispensing of study drug, return of unused study drug, and return of empty study drug bottles. A three month supply (3 bottles) of study drug is dispensed at the rz, f12, f24, f36, f48 and f60 visits. The patient should be instructed to take one capsule daily.

The patient should be queried about return of empty study drug bottles at all study visits. Each time a patient returns used study drug bottles to the clinical center, the clinical coordinator should count and record the remaining number of capsules in the study drug bottles. This form allows recording of the return of up to four bottles. If more than four bottles are returned at a time, complete a second form (using visit code "n") to record the information for the remaining bottles.

Α.	Center,	patient,	and	visit	identification	

- 1. Center ID: _____ ___ ____
- 3. Patient code:
- 4. Date of visit:

-		-
day	mon	year

5. Visit code:

6. Form & revision: r d	1
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7. Study: FLINT <u>7</u>

B. Study drug dispensing

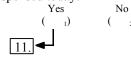
- 8. Is this a second form for returning additional drug bottles at this visit:

 Yes

 No

 (*_1)

 (_2)
 - * Key first form before this form.
- **9.** Will study drug be dispensed today:



- **10.** Reason for not dispensing study drug *(check all that apply)*
 - a. Not a scheduled study drug dispensing visit: (1)
 - **b.** Study physician-directed treatment interruption/termination: (1)
 - c. Unwillingness of the patient to take study drug:
 - **d.** Other (specify):

specify	
	16. ◀

11. How many bottles were dispensed: (1-3)

Bottle tear-off label

12.	[
	Affix label here
	<u> </u>





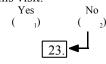
Patient ID:		

15.	How was the study drug dispensed to the
	patient (check only one):

In person		(1)
Mail		(2)
Other (specify)		(3)
	specify		

C. Study drug return

16. Were any bottles returned at this visit:



17. Number of bottles returned (*if more than 4 bottles are returned, complete a second RD form*):

(1-4)

	a. Bottle No.	b. Number of capsules returned
18.		(00-40)
19.		(00-40)
20.		(00-40)
21.		(00-40)

D. Remaining bottles

22. Are any additional bottles being returned:

, returned.	
Yes	No
(* 1)	(,

*If yes, complete a second RD form using visit code "n."

L. Auministrative miormano	Ε.	Adminis	strative	information
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- 23. Study Physician PIN:
- **24.** Study Physician signature:
- **25.** Clinical Coordinator PIN:
- **26.** Clinical Coordinator signature:

27. Date form reviewed:

-		
day	mon	year

RG - Registration

Purpose: To register patients as candidates for enrollment in the FLINT trial and to assign a patient ID number. This is the first form completed for a FLINT patient. The Registration Form must be the first form keyed, before any other FLINT forms are keyed.

When: At first screening visit s.

Administered by: Clinical Coordinator.

Respondent: Patient.

Instructions: Use Flash Cards as instructed. Do not assign a patient ID if patient has previously been assigned an ID for a NASH CRN study or if an condition is checked in section B or C.

A. Center, patient and visit identification	10. Gender:	
4.6	Male (1)
1. Center ID:	Female (2	2)
2. Patient ID:	11. Ethnic category (show the patient Flash Card # and ask the respondent to pick the category the describes the patient best; check only one):	<u>!]</u> at
3. Patient code:	Hispanic or Latino or Latina (1)
4. Visit date:		2)
day mon year 5. Visit code: S 6. Form & revision: r g 1	12. What describes your Hispanic, Latino, or Latina origin best (show the patient Flash Card # and ask the respondent to pick the subcategory the best describes their Hispanic, Latino, or Latin origin; check only one):	at
	Mexican (1)
7. Study: FLINT <u>7</u>	Puerto Rican (2	2)
•	Cuban (3	3)
B. Consent	South or Central American (4)
8. Has the patient signed the FLINT informed consent statement:	Other Spanish culture or origin (₅)
Yes (No 2) C. Information about patient	specify 13. Racial category (show the patient Flash Card # and ask the respondent to pick the category of categories that describe the patient best; check a that apply)	or
Or annound mooned process	a. American Indian or Alaska Native:	1)
9. Patient age	b. Asian:	1)
a. Date of birth:	c. Black, African American, Negro, or Haitian:	1)
day month year Record 4-digit year for date of birth.	d. Native Hawaiian or other Pacific Islander:	1)
b. Age at last birthday:	e. White:	1)
c. Is patient at least 18 years of age: Yes No	f. Patient refused:	1)
$\begin{pmatrix} 1 \end{pmatrix} \begin{pmatrix} 2 \end{pmatrix}$)	

14. In what country was the patient born <i>(check only one):</i>			only	20. Marital status of the patient (show the patient Flash Card #5 and ask the respondent to pick the category that describes the			
	Continental US (includes Alaska) or Hawaii	(`	patient best; check only one):	,,,,		
	Other, (specify):	(1) 2)	Single, never married (1)		
			2 <i>)</i>	Married or living in marriage-like relationship (2)		
	specify			Separated, divorced, or annulled (3)		
15	Highest educational level achieved by			Widowed (4)		
10.	patient (show the patient Flash Card #3 the respondent to pick the category that the patient best; check only one):			21. Combined annual income before taxes of all members of patient's household	1		
	Never attended school	((0	(show the patient/parent Flash Card #6 and a the respondent to pick the category that describ			
	Kindergarten, pre kindergarten, or younger	(1)	the patient's combined household income be check only one):	?st;		
	Grades 1 to 5	(2)	Less than \$15,000 (1)		
	Grades 6-8	(3)	\$15,000 - \$29,999 (2)		
	Grades 9-11	(4)	\$30,000 - \$49,999 (3)		
	Completed high school	(5)	\$50,000 or more	4)		
	Some college or post high school education or training	(6)	D. Previous registration in a NASH CRN study			
	Bachelor's degree or higher	(7)	22. Has the patient ever been assigned an ID number in a NASH CRN study:			
16.	Is the patient currently employed:	,	. T	$\binom{\text{Yes}}{1} \qquad \binom{N}{1}$	ю 、		
	$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix}$	(No 2)		₂)		
	1	<u>9.</u>	_ ً	26.	J		
17.	What is the patient's current occupation:			23. In which NASH CRN studies has the patient previously been registered <i>(check all trapply)</i>	hat		
	specify occupation			a. NAFLD Database:	1)		
10				b. PIVENS:	1)		
18.	About how many hours does the patient work each week:			c. TONIC:	,)		
		# hour	S	d. NAFLD Adult Database 2:	1)		
10	Which of the following categories best			e. NAFLD Pediatric Database 2:	1)		
17.	characterizes the patient's occupational				1) \		
	history (show the patient/parent Flash Ca ask the respondent to pick the category scribes the patient best; check only one).	that	and de-	f. Other, (specify):	1)		
	Never employed	((0	specify			
	Laborer	(1)	24. ID Number previously assigned to patient (reco	ord		
	Clerical	(2)	patient ID in item 2):	na		
	Professional	(3)		—		
	Homemaker	(4)	25. Code previously assigned to patient (record p	oa-		
	Other, (specify):	(5)	tient code in item 3):			
	specify				1		
	эрсспу			<u> 27.</u>	J		

Patient ID:		
rauciii iD.	 	

E. ID assignment

(If a STOP condition was checked in section B or C, the patient is ineligible and a Patient ID should not be assigned. If the patient was previously registered in a NASH CRN study, a new ID number should not be assigned.)

26. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####, zzz

F. Administrative information

27. Clinical Coordinator PIN: ____ ___

28. Clinical Coordinator signature:

29. Date form reviewed:

day mon year

RZ - Randomization Checks

Purpose: To check eligibility for FLINT with respect to items not checked elsewhere on FLINT screening forms and record reasons for ineligibility for patients found to be ineligible.

When: Visit rz

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: This form may be initiated at any time. If the patient proceeds to randomization, it must be reviewed on the day of randomization. Patients of childbearing potential must complete the randomization day pregnancy test at the clinic on the day of randomization. Patients who are not of childbearing potential may complete the randomization day visit over the telephone. If this is the case, these requirements must be followed:

- (1) If your consent statement has an area for affirmation of consent prior to randomization, the patient should have signed the affirmation at his/her last screening visit.
- (2) The clinical coordinator must confirm with the patient by telephone on the day of randomization, that the patient feels well and continues to consent to randomization.
- (3) The assigned study medication must be mailed to the patient on the day of randomization for delivery the next day.
- (4) The patient should be instructed to start the medications as soon as possible after receipt.

r z 2

FLINT 7

If \mathfrak{S} is checked for any item, complete the entire form, but note that the patient may not continue in the FLINT trial. If an item has not been assessed because the patient is ineligible, write "m" (missing) next to that item. This form should be keyed for each patient for whom form RG was completed.

Δ	Center	patient.	visit	and	study	ident	tificati	Λn
A.	Center,	pauent	VISIL,	anu	stuuv	Iuen	uncau	UH

1.	Center ID:				
2.	Patient ID:				
3.	Patient code:				
4.	Visit date (date this form	is initi	ated):		
		mon		ye	ear

- **6.** Form & revision:
- 7. Study:

5. Visit code:

B. Diabetes Status

8. In the judgment of the Study Physician and based on the patient's medical history and laboratory results, does the patient have diabetes:

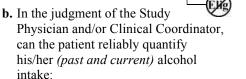


9. Is the patient's diabetes uncontrolled (HbA1c greater than or equal to 9.5% within the past 60 days):



C. Alcohol use exclusions

- 10. Alcohol use
 - a. On average, has the patient consumed more than 30 g/day of alcohol (males) or 20 g/day of alcohol (females) for a period of more than 3 consecutive months in the 12 months prior to screening:



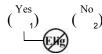


D. Laboratory test exclusions

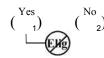
- 11. Hepatic Decompensation
 - **a.** Is the patient's serum albumin less than 3.2 g/dL:



b. Is the patient's INR greater than 1.3:



c. Is the patient's direct bilirubin greater than 1.3 mg/dL:



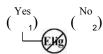
d. Does the patient have a history of esophageal varices, ascites, or hepatic encephalopathy:



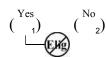
- 12. Other laboratory measures
 - a. Is serum ALT greater than 300 U/L:



b. Is serum creatinine greater than or equal to 2.0 mg/dL:



c. Is the platelet count less than 100,000 mm³:



d. Tests are outside time window and clinic chose not to repeat tests:



E. Medication use exclusions

13. Use of drugs associated with NAFLD for more than 2 weeks in the past 12 months:

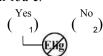


F. Other chronic liver disease exclusions

14. Does the patient have ongoing autoimmune liver disease defined by liver histology:



- **15.** Does the patient have primary biliary cirrhosis defined by at least two of the following criteria *(check all that apply)*
 - **a.** Alkaline phosphatase above the upper limit of normal:
 - **b.** Presence of antimitochondrial antibody (AMA): (1)
 - c. Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts:
 - **d.** Were two criteria checked in 15a-c:



1)

16. Does the patient have known primary sclerosing cholangitis:



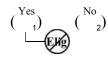
17. Does the patient have Wilson's disease defined by ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



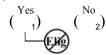
18. Does the patient have alpha-1-antitrypsin (A1AT) deficiency defined by a suggestive liver histology confirmed by A1AT level less than normal (physician judgment):



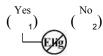
- 19. Hemochromatosis
 - **a.** Does the patient have a history of hemochromatosis:



b. Does the patient have iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:



- **20.** Do any of the patient's assessments show evidence of other chronic liver disease
 - **a.** Drug induced liver disease as defined on the basis of typical exposure and history:



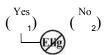
b. Known bile duct obstruction:



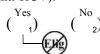
c. Suspected or proven liver cancer:



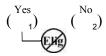
d. Hepatitis B (HBsAg):



e. Hepatitis C (HCV RNA or anti-HCV):



f. Any other type of liver disease other than NASH that warrants exclusion from the trial:



G. Liver biopsy exclusions

21. Presence of cirrhosis on liver biopsy:



22. Inability to safely undergo a liver biopsy:



23. Biopsy out of window and patient chose not to repeat:



24. Biopsy inadequate for scoring and patient chose not to repeat:



25. Local pathologist did not find borderline or definite steatohepatitis:

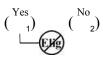


26. NAFLD activity score (NAS) less than 4 or any subscore (steatosis, ballooning, lobular inflammation) equal to 0:

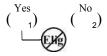


H. Other medical exclusions

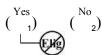
27. History of bariatric surgery or plans to have bariatric surgery during the FLINT trial:



28. History of biliary diversion:



29. Known positivity for HIV infection:



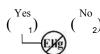
30. Known active, serious medical disease with a likely life-expectancy of less than 5 years:



31. Known active substance abuse (inhaled or injected) in the past 12 months:



32. Participated in an IND trial in the past 30 days:

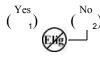


33. Other conditions which, in the opinion of the investigator, would impede compliance or hinder completion of the study:



I. Birth control exclusion

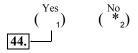
34. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient *(female of childbearing potential)* willing to use effective birth control methods to avoid pregnancy during the 72 weeks of treatment *(check "Yes" if patient is male or not of childbearing potential):*



J. Eligibility check on day of randomization

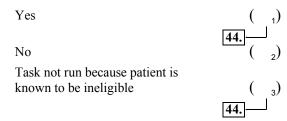
(do in person if patient is of childbearing potential; otherwise, these checks may be done over the telephone with the patient on the day of randomization)

35. Was an ineligibility condition checked or an eligibility not ascertained in items 9-34:

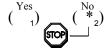


*Key forms RG, AD, BG, BP, CG, HF, LD, LR, LS, MR, PE, QF, and SD. Run the Randomization Task on your clinic data system.

36. Were any stops or ineligible conditions other than "missing form RZ" identified by the Randomization Task:

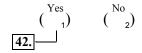


37. Does the patient feel well today:

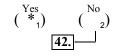


*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

38. Is the patient male:



39. Is the patient of childbearing potential:



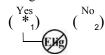
*Administer pregnancy test.

40. Is the patient pregnant (positive pregnancy test on the day of randomization):



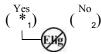
*Go to item 44.

41. Is the patient currently breast feeding



*Go to item 44.

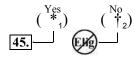
42. In the Study Physician's judgment, is there any reason to exclude the patient from randomization:



*If Yes, specify reason and then go to item 44:

specify reason

43. Does the patient still consent to randomization (you should ask the patient to orally affirm his/her consent):



*Go to item 45 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.

†Complete items 44-49 and key the form. The form must be keyed to document the reasons for ineligibility for FLINT.

K. Reasons for ineligibility for ineligible patients

Note: Complete this section for ineligible patients only.

- **44.** Reason for ineligibility (check all that apply)
 - **a.** Reason covered in items 9-43:
 - **b.** Other reason not covered on this form (specify):

specify

- L. Administrative information
- **45.** Study Physician PIN:

46. Study Physician signature:

7	Clinical	Coordinator PIN:	
	CHIIICAL	COOLUMNIOLE IN	

48. Clinical Coordinator signature:

49. Date form reviewed

(Note re: This form must be reviewed on the day of randomization; if it was keyed prior to the randomization day, update it, re-review it on the day of randomization, and key the revised date of review.):

day	mon	year

(NOTE: If patient was not present in the clinic to receive the assigned medication, ship the medication to the patient by overnight delivery service.)

SD - Liver Biopsy Materials Documentation

Purpose: To document that the liver biopsy required for screening was obtained under the time and medication restrictions required by the protocol and to document whether liver tissue was obtained for banking (both screening and followup biopsies). The number and type of slides available for archival at the Data Coordinating Center is noted for both screening and followup biopsies. If slides cannot be archived at the Data Coordinating Center, the source of the slides and the time by which the slides must be returned to the clinical center are recorded.

When: Visits s, f72, and as needed for biopsies at interim times.

By whom: Clinical Coordinator in consultation with the Study Pathologist.

Instructions: This form provides information about the tissue and slides from the biopsy and alerts the DCC to expect completion of the Liver Tissue Banking (LT) form, receipt of tissue at the Biosample Repository, and receipt of slides from the biopsy at the Data Coordinating Center. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and code, and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60, the borrowed slides should be labeled with removable overlabels with sequence numbers 81-90.

Δ	Center	natient a	nd visit	identi	fication
A.	Center.	Dauent a	mu visit	IUCILLI	псаноп

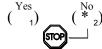
- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___
- **3.** Patient code: ____ ___
- 4. Date form initiated:

day	mon	year

- **5.** Visit code: ____ ___
- **6.** Form & revision: _s__d__2__
- **7.** Study: FLINT 7

B. Surgical pathology report

8. Is a copy of the report annotated with the patient's NASH CRN ID number and code and with name blacked out attached to this form:



* Obtain a copy of the report, annotate it, and attach it. You can use one of the pathology labels to annotate the report.

9. Biopsy information

a. Date of biopsy specified on the surgical pathology report:

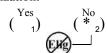
			_		_
	day		mon		year
_	_				

b. Lobe specimen obtained from *(check only one)*:

Right	(1.
Left	(2
Unknown	(•

C. Requirements for screening biopsy

- **11.** Is the date in item 9a within 90 days of the anticipated date of randomization:



* Biopsy date must be within 90 days of randomization.

D. Biopsy specimens and stained slides at the clinical center

12. Was a sample of liver tissue obtained for banking:

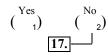
 $\binom{\text{Yes}}{*}$ $\binom{\text{No}}{2}$ * If Yes, complete the Liver Tissue Banking (LT)

13. What stained slides from the biopsy are available at the clinical center (check all that apply)

a. H & E stain:	(1)
a. II & E stain.	(1)

E. Unstained slides to be sent to the DCC

14. Are unstained slides available for sending to the DCC:



- 15. How many unstained slides will be sent to the DCC:
- **16.** What are the slide sequence numbers for those slides (from the NASH CRN labels on each slide - use permanent labels, sequence numbers 01-60):

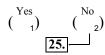
a. Slide sequence number	
-	01-60
b. Slide sequence number	01-60
c. Slide sequence number	
1 01:1	01-60
d. Slide sequence number	01-60

- e. Slide sequence number 01-60
- **f.** Slide sequence number 01-60
- **g.** Slide sequence number 01-60
- h. Slide sequence number 01-60
- i. Slide sequence number 01-60
- i. Slide sequence number 01-60

F. Stained slides to be sent to the DCC

(The institution's stained slides must be sent to the DCC only if fewer than 3 unstained slides will be sent to the DCC)

17. Are any stained slides to be sent to the DCC:

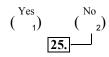


- 18. How many stained slides are to be sent to the DCC:
- 19. Sequence number of slides to be sent to
 - a. Slide sequence number of H & E stain:

- **b.** Slide sequence number of Masson's trichrome stain: 81-90
- **c.** Slide sequence number of iron stain:

d. Slide sequence number of other stain:

20. Are any stained slides to be returned to the clinic:



- 21. How many stained slides are to be returned to the clinic:
- 22. List sequence numbers of those slides to be returned
 - **a.** Slide sequence number:

81-90
81-90
81-90

b. Slide sequence number: c. Slide sequence number:

01	,,	
81	-90	

- **d.** Slide sequence number:
- 23. When do the stained slides need to be returned to the clinical center (check only one):

immediately after central review
At the end of the NASH CRN funding
mania d

(1)

24. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department

Other, (specify):

name

address

Note: this is the FLINT trial record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

address

phone

\sim	A .1	• . • . 4	4 •	· C	4
J.	Aam	unist	rative	nior	mation

- **25.** Clinical Coordinator PIN: ____ ___
- **26.** Clinical Coordinator signature:
- **27.** Date form reviewed:

_		_
day	mon	year

SR - Serious Adverse Event/IND Safety Report

Purpose: To report serious adverse events recorded on the Interim Event Report (IE) form that satisfy the FDA expedited FDA Safety Report requirements outlined in the FLINT Trial protocol. In order to satisfy FDA expedited IND Safety Report requirements the event must be SERIOUS, UNEXPECTED, AND have a REASONABLE POSSIBILITY of being caused by FLINT study drug, as defined by Title 21 Code of Federal Regulations Part 312.32 IND Safety Reporting:

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "SERIOUS" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "REASONABLE POSSIBILITY" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "**UNEXPECTED**" if it is not listed in the obeticholic acid investigator's brochure or is not listed at the specificity or severity that has been observed for your patient.

When: The SR form should be used only for reporting a serious and unexpected adverse event which meets the IND Safety Report criteria as stated above, or when a followup report is needed for a previously completed SR form. When the serious adverse event does not meet the expedited IND Safety Report criteria, use the Interim Event Report (IE) form to report the event.

Completed by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form **within 2 business days**. The short name (item 24) and the severity grade (item 25) are to be obtained from the NCIs Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. (Click on Studies then click on FLINT). Report the serious advere event to your IRB per local guidelines. Send the Data Coordinating Center the following:

- 1) A copy of this SR form and corresponding IE form
- 2) A narrative description of the event that includes all of the information provided on the SR and IE forms and a justification of why the event is serious, unexpected and has reasonable possibility of being caused by FLINT study drug (see FLINT SOP I, section 6.16).
- 3) A copy of your report to your IRB, if applicable

The Data Coordinating Center will submit a preliminary copy of the report to NIDDK (Sponsor) for further review within 3 business days. If NIDDK staff determines that an expedited IND Safety Report is required, a final report will be submitted to the FDA (within 15 days). Intercept Pharmaceuticals (manufacturer of study drug), the DSMB, and Steering Committee will be notified of all serious adverse events requiring an expedited IND safety report within 7 days of keying the SR form. For more information, see FLINT SOP I, section 6.16.

Followup report: A followup report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patients condition or in the physicians judgment about the event since the previous report was filed.

A. Center, patient and visit identification		4. Date of report:			
1. Center ID:				year	
2. Patient ID:		5. Visit code: If report not associate	d with a visit, fil	l in ''n.''	
3. Patient code:		6. Form & revision:	_S_	_r3_	
		7. Study:	FL	INT <u>7</u>	

1)

B. Participant information

8. Date randomized in FLINT:

day	mon	year

9. Gender:

Male	(1)
Female	(2)

10. Age at time of adverse event:

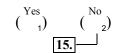
years

C. Determination of an serious adverse report

11. Is there evidence to suggest a causal relationship between FLINT study drug and the adverse event:

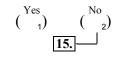
Definitely yes	(1)
Probably yes	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
Possibly yes	$\begin{pmatrix} & & \\ & & \end{pmatrix}$
Probably no	(4)
Definitely no	15

12. Is this a serious adverse event:



If Yes, then select all the reasons that apply:

- **a.** Severity Grade 4 or 5:
- **b.** Required inpatient hospitalization or prolonged existing hospitalization: (1)
- c. Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions: (1)
- e. Congenital abnormality or birth defect: (
- 13. Is this an unexpected adverse event:



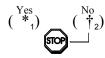
14. Reason the adverse event was unexpected:

Not listed in the obeticholic acid investigator brochure

Listed in the obeticholic acid investigator's brochure, but not at the specificity or severity that has been observed

Listed in the obeticholic acid investigator's brochure as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with previous experience of obeticholic acid (

15. Did you select "Yes" for items 11, 12, and 13:



*NIDDK will determine if an expedited IND Safety Report will be submitted to the FDA within 15 calendar days.

†Use FLINT forms HI and IE to report adverse events that are not serious, not associated with the FLINT study drug, or are expected. Do not key this form.

D. Serious adverse event description

16. Is this the first report or a followup report for this serious adverse event:

First report

Followup report (2

17. Date of serious adverse event onset:



18. Date serious adverse event was reported to clinical center:

_		_
day	mon	year

19. Describe the serious adverse event:

	FLINT stu		nents other than se at the time of	
21.	Specify tests/treatments and comorbidities:		s and	
22.	Was an uns	scheduled liv	ver biopsy	
	performed:		$\begin{pmatrix} \text{Yes} \\ * \\ 1 \end{pmatrix}$	(No
		copy of the it he SR form.	nstitutional pathol	
23.	Did the ser significant		e event result in	(No 2)
	Specify:		<u>2</u>	4. — "
24.	(short nam CTCAE v3 at www.na	nes for AEs a 3.0 document	click on Studies	

25. Severity grade (severity grades are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Studies and then click on FLINT):

Grade 3 - Severe (1)

Grade 4 - Life threatening or

disabling (2
Grade 5 - Death (*2

*Complete and key the Death Report (DR) form.

26. Current status of serious adverse event *(check only one):*

Resolved (1)
Active (2)
Unknown (3)

27. Date resolved:

day mon year

28. Additional comments on serious adverse event:

17	A .1	:_	•	4:	: C	mation
н	An	mın	istra	tive	intor	mation

29.	Study Physician PIN:		
30.	Study Physician signature:		
31.	Clinical Coordinator PIN:		
32.	Clinical Coordinator signature:		
33.	Date form reviewed:	_	

Key this form and send the DCC within 2 business days:

mon

year

- (1) A copy of this SR form(2) A narrative description of the serious adverse event
- (3) A copy of your report to your IRB.

We are asking for copies of these reports on serious adverse events so that we assure appropriate and timely study wide review. The serious adverse event report will be reviewed by Dr. Jeanne Clark, the Safety Officer, and NIDDK (Sponsor).

Transfer Notification

Purpose: To record a transfer from one center to another center.

When: Upon transferring to the enrolling center and prior to the first visit at the adopting center.

By whom: Clinical coordinator of each center (enrolling center: sections A-C, adopting center: sections D- E).

Instruction: For enrolling center: When patient notifies enrolling center of upcoming transfer, the enrolling clinical coordinator should (1) complete Sections A-C of the Transfer Notification (TN Form), (2) send the TN form to the adopting center, with a copy of the most recently completed HI, LR, RD, and PE/PF forms, (3) send the labels for cryovials and slides and a copy of the visit window schedule to the adopting center. **For adopting center:** Prior to the patient coming to the adopting center, the adopting clinical coordinator should: (1) complete Sections D-E of the TN form, (2) Fax the TN form to the DCC (Fax: 410-955-0543). The DCC will key the form.

A. Enrolling center and patient identification	D. Adopting center, patient and visit identification		
1. Center ID:	14. Adopting center ID:		
2. Patient ID:	15. Patient ID (must be same as in Section A):		
3. Patient code:4. Date of notification of intent to transfer:	16. Patient code: (must be same as in Section A):		
	17. Expected date of first followup visit at adopting center:		
6. Form & revision:t n 1	day mon year		
7. Study: FLINT 7	18. Visit ID code for expected first followup visit at adopting center: f		
B. Last followup visit information8. Date of last followup visit:	Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.		
day mon year	E. Adopting center administrative information		
9. Visit ID code of last completed followup visit:	19. Date form reviewed:		
10. Have cryovial and slide labels been sent to the adopting center:	day mon year 20. Clinical coordinator ID:		
*Send the cryovial and slide labels to the adopting center.	21. Clinical coordinator signature:		
C. Enrolling center administrative information 11. Date form reviewed:	Fax form to the DCC. The DCC will key the TN form.		
day mon year			
12. Clinical coordinator ID:			
13. Clinical coordinator signature:			

NASH CRN CyNCh

CyNCH Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
AE	Adverse Event Report
ВН	Baseline History
BP	Blood Processing for Plasma and Serum
CG	Genetic Consent and Blood Collection Documentation
CO	Database Closeout/Closeout Form
CR	Central Histology Review
DD	DEXA Scan for Bone Mineral Density
DR	Death Report
FH	Follow-up Medical History
HF	Liver Biopsy Histology Findings
LP	Symptoms of Liver Disease (Children)
LR	Laboratory Results - Tests Done at s1 and During Followup
LS	Laboratory Results - Tests Done Only During Screening
LT	Liver Tissue Banking
MR	MRI Report
MV	Missed or Incomplete Visit
ND	Nutrition Data Documentation
PE	Physical Examination
PF	Focused Physical Examination
PQ	Pediatric QOL: Parent Report for Teens (Age 13-17)
PR	Pediatric QOL: Parent Report for Children (Age 8-12)
PW	Pediatric QOL: Child Report (Age 8-12)
PY	Pediatric QOL: Teen Report (Age 13-17)
RC	Rescreen Form
RD	Study Drug Dispensing and Return
RG	Registration
RZ	Randomization Checks
SD	Liver Biopsy Materials Documentation
SR	Serious Adverse Event/IND Safety Report
TN	Transfer Notification

A

AD – Alcohol Use Disorders Identification Test (AUDIT)

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.

When: Visit s.

Administered by: Self-administered (age 13 or older), interviewer administered (age 8-12). Clinical Coordinator must be available at visits to answer questions and review completed forms.

Respondent: Patient, age 8 or older. Patients age 13 or older should complete the form without help from family. Clinical Coordinator/parent can assist patients age 8-12.

Instructions: Flash Card #9, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator then should complete section B below.

. Ce	enter, patient, and vi	isit identi	ficatio	n				strative information		
1.	Center ID:					(To be completed by Clinical Coordinator after survey is completed.)			ator ajter	
2.	Patient ID:			·		8.	How	was the questionnaire comple	eted:	
3.	Patient code:						Self-	-administered by patient	(1)
4.	Date of visit (date p	oatient co	mplete	d the forn	ı):				<u>10.</u> ◀	_
	day	mon		yea	r			rview in English rview with translator	(2) 3)
5.	Visit code:		<u>s</u>	. <u> </u>		9.	Who	was the respondent (check all	! that apply):	:
6.	Form & revision:		<u>a</u>	<u>d</u>	1_		a. b.	Patient: Patient's mother or female gu		1) 1)
7.	Study:			CyNCh	n <u>8</u>		c. d.	Patient's father or male guard Other (specify):	lian: (1) 1)
								specify		
						10.	Clina a. b.	ical Coordinator PIN: Signature:		
						11.	Date	e form reviewed:		
								day mon	year	

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below (*items 1-11 are for clinical center use only*).

12. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times a month	Two to three times a week	Four or more times a week
(0)	(1)	(2)	(3)	(4)
<u> </u>				

13. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7 to 9	10 or more
(0	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	(₂)	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

14. How often do you have six or more drinks on one occasion?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
(0	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	(4)

15. How often during the last year have you found that you were not able to stop drinking once you had started?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

16. How often during the last year have you failed to do what was normally expected from you because of drinking?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(3)	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$

Patient ID:		

17. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
(0)	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	(4)

18. How often during the last year have you had a feeling of guilt or remorse after drinking?

Less than				Daily or
Never	monthly	Monthly	Weekly	almost daily
(0	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	(4)

19. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

	Less than			Daily or
Never	monthly	Monthly	Weekly	almost daily
$\begin{pmatrix} 0 \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 4 \end{pmatrix}$

20. Have you or someone else been injured as a result of your drinking?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

21. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

	Yes, but not in	Yes, during
No	the last year	the last year
$\begin{pmatrix} & & \\ & & \end{pmatrix}$	$\begin{pmatrix} & & 1 \end{pmatrix}$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$

22. Today's date:

 $Thank\ you\ for\ completing\ this\ question naire.$

CyNCh

AE - Adverse Event Report

Purpose: To document an adverse event that threatens the integrity of the CyNCh trial or well-being of a study participant that includes, but not limited to:

- (1) events that impact the patient's treatment or participation in CyNCh
- (2) adverse events that may or may not be related to study drug
- (3) other events that clinical center staff feel should be reported
- (4) when a follow-up report is needed for a previously completed AE form

As defined by Title 21 Code of Federal Regulations Part 312.32 *IND Safety Reporting*: *Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other medical events may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

When: All visits. Use visit code if reporting an event discovered during a regular follow-up visit. Use visit code n if event is discovered between study visits. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code for first event, n for second event, n2 for third event, etc. Adverse events that are serious, unexpected and have reasonable possibility of being caused by CyNCh study drug should also be recorded on the Serious Adverse Event/IND Safety Report (SR) form.

Completed by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for every visit. The short name (item 19) and the severity grade (item 20) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Studies and then CyNCh. Fax the DCC (Fax 410-955-0932; Attention: Pat Belt) a copy of this form if severity grade is 3 or higher within 1 week for further review by Dr. Jeanne Clark, the NASH CRN Safety Officer. For more information, see SOP I sections 6.18 and 6.19.

Follow-up report: A follow-up report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patient's condition or in the physician's judgment about the event since the previous report was filed.

A. Center, patient, and	visit identification	5. Visit code: if report not associated v	vith a visit. fill in "n"
1. Center ID:		y · · · · · · · · · · · · · · · · · · ·	, y
		6. Form & revision:	<u>a</u> <u>e</u> <u>1</u>
2. Patient ID:			C NCL 0
		7. Study:	CyNCh 8
3. Patient code:			
4. Date of report:			
day	mon year		

B. Visit interval identification

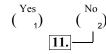
8. Since the last visit, has the patient had a reportable event:

(Y	res 1	(No 2)
		33.	ل

9. Most recently completed visit prior to adverse event

a. Date:		
day	mon	year

- **b.** Visit code: ____ ___
- **10.** Since the last visit, has the patient had any ER visits or hospitalizations:



If Yes, specify reason and list dates:

If none for items 10a or 10b, enter "00".

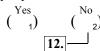
a. Number of hospitalizations:

hospitalizations

b. Number of Emergency Room visits:

# visits	

11. Since the last visit, has the patient had any health problems not already reported:



If Yes, specify health problem and list dates:

\sim	Dation	4	inform	a4: am
١.,	ratien	L	inform	ation

12. Gender:

Male	(1)
Female	(2)

13. Age at time of event:

D. Event description

14. Is this the first report or a followup report for this adverse event:

First report	(1)
Followup report	(2)

15. Date event started:

day	mon	year	

16. Nature of event (check all that apply)

a.	Drug	dispensing	mixup:		1)
----	------	------------	--------	--	----

f. Worsening of a co-morbid illness:
$$\binom{1}{1}$$

^{*}CyNCh study drug will be discontinued if a patient becomes pregnant. Contact the NASH CRN Data Coordinating Center to unmask the study drug.

17. Describe event:			20. Severity grade:	
			Not an adverse event (0
			Grade 1 - Mild (1)
			Grade 2 - Moderate (2)
			Grade 3 - Severe (3)
			Grade 4 - Life threatening or disabling (Grade 5 - Death (4) *5)
			*Complete and key Death Report (DR) form.	3/
For items 18, 19, and 20, please refer to (21. Randomization in CyNCh	
v3.0 available at www.nashcrn.com; click and then CyNCh.	on Studie	es	a. Has patient been randomized in CyNCh:	
18. Identify body system (check all that of	apply)		$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix}$	No)
a. Auditory/ear:	(1)	29.	
b. Allergy/immunologic:	(1)	b. Date randomized in CyNCh:	
c. Ocular/visual:	(1)		
d. Hepatobiliary/pancreatic:	(1)	day mon year	
e. Infection:	(1)	22. Is the patient currently receiving the	
f. Constitutional symptoms:	(1)	CyNCh study drug:	No .
g. Psychiatric:	(1)	$\binom{\text{Yes}}{1}$	2)
h. Cardiovascular:	(1)	23. Patient's history of treatment with	
i. Dermatologic/skin:	(1)	CyNCh study drug	
j. Endocrine/metabolic:	(1)	a. How long has patient been on study drug:	
k. Gastrointestinal/digestive:	(1)	urug.	
l. Lymphatic/blood:	(1)	b. What daily dose was the patient	
m. Musculoskeletal:	(1)	taking prior to the adverse event:	
n. Neurologic:	(1)		
o. Pulmonary/respiratory:	(1)	mg/day	
p. Renal/genitourinary:	(1)	c. Have there been any treatment interruptions or restarts:	
q. Sexual/reproductive:	(1)	Yes	No 2)
r. Other (specify):	(1)	Include stop/restart dates and reasons:	2)
specify other body system				—
s. None of the above:	(1)		
19. Short name for event if applicable:				_
Not applicable	(0		

24. Is there evidence to suggest a causal
relationship between the CyNCh study
drug and the adverse event:
D 7 1 1

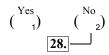
Definitely yes	(1)
Probably yes	(2)
Possibly yes	(3)
Probably no	(4)
Definitely no	(_)

25. Is this a serious adverse event:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	26.
_	

If Yes, then select all the reasons that \overline{apply} :

- **a.** Severity Grade 4 or 5:
- **b.** Required inpatient hospitalization or prolonged existing hospitalization: (1)
- **c.** Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions: (1)
- **d.** Jeopardized patient and required medical or surgical intervention to prevent a serious event:
- e. Congenital anomaly or birth defect: (1)
- **26.** Is this an unexpected adverse event:



27. Reason the adverse event was unexpected:

Not listed in the cysteamine bitartrate investigator's brochure

Listed in the cysteamine bitartrate investigator's brochure, but not at the specificity or severity that has been observed

Listed in the cysteamine bitartrate investigator's brochure as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with previous experience of cysteamine bitartrate

28. Did you select "Yes" for items 24 (definitely, probably, or possibly), 25, and 26:

Yes	No
$(*_1)$	(2
	4 1

*If Yes, please also complete a Serious Adverse Event/IND Safety Report (SR) form and follow instructions.

29.	Current	status	of ac	lverse	event	(check	only	one)	
۷).	Current	status	or ac	110130	CVCIII	(CHECK	omy	one)	•

Resolved	(1)
Active	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
Unknown	31. (₃)
	31.

30. Date adverse event resolved:

_		_
day	mon	year

31. What action was taken:

-	
-	

32. Other comments on event:

_				
_				
-				
_				

Dationt ID:			
Patient ID:	 	$\overline{}$	

E. Administrative information
33. Clinical Coordinator PIN:
34. Clinical Coordinator signature:
35. Study Physician PIN:
36. Study Physician signature:
37. Date form reviewed:

Key this form and fax the DCC (Attention: Pat Belt) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious adverse events so that we assure appropriate and timely NIDDK review. The serious adverse event reports will be reviewed by Dr. Jeanne Clark, the Safety Officer.

mon

year

BH - Baseline History

Purpose: To collect baseline history information about the patient.

When: Visit s.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient or patient's parent.

Instructions: Collect information by interview or chart review. If <u>c</u> is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for CyNCh. If <u>w</u> is checked for an item, the patient is ineligible and cannot enroll in CyNCh. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

Α.	Center,	visit.	and	natient	identif	fication
△ •	conta,	V 131t,	anu	patient	iuciiui	ncanon

1. Center ID:				
---------------	--	--	--	--

- **2.** Patient ID: ____ ____
- **3.** Patient code: ____ ___
- **4.** Visit date (date this form is initiated):

-	_	_
day	mon	year

5. Visit code:

- _S____
- **6.** Form & revision:
- _b_ h_ _1_

7. Study:

B. NAFLD history

8. Does the patient have a liver biopsy done that you want evaluated for the CyNCh trial (complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy):

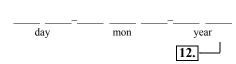


*Randomization must be done within 120 days of liver biopsy.

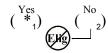
9. Date of liver biopsy:

day	mon	ye	ear

10. Last day to randomize based on liver biopsy date (120 days after biopsy; use date calculator 2 on the NASH CRN home page):



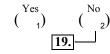
11. Will the patient have a biopsy during screening:



*Blood draw for banking should be done **prior** to the biopsy or at least 4 days **after** the biopsy.

C. Menstrual history and use of effective birth control

12. Is the patient female:



- 13. Menarche history
 - **a.** Has menarche occurred:

b. What was the patient's age at menarche:

	_	
age	in	years

14. Characterize the menstrual history in the past year *(check only one):*

Regular periods (1
Irregular periods (2
Rare periods (3

No periods (

15. Is the patient of childbearing potential:



16. Is the patient currently pregnant:



17. Is the patient currently breastfeeding:



*Caution: Patient cannot be breastfeeding at time of randomization.

18. If sexually active, is the patient willing to use two effective birth control methods during CyNCh:



- **D. Medical history** (means Caution; condition is exclusionary if study physician agrees with diagnosis)
- 19. Has the patient ever been diagnosed with or treated for any of the following (check all that apply; source of information can be interview and/or chart review)
 - **a.** Diabetes type 1:
 - **b.** Diabetes type 2:

*If HbA1c is > 9%, patient is ineligible.

c. Hepatitis B:



d. Hepatitis C:



e. Autoimmune hepatitis:



f. Autoimmune cholestatic liver disorder (PBC or PSC):



g. Wilson's disease:



h. Alpha-1-antitrypsin (A1AT) deficiency:



i. Hemochromatosis or iron overload:



j. Drug induced liver disease:



k. Ascites:



I. Gilbert's syndrome:



m. Esophageal or gastric varices on endoscopy:



n. Bleeding from varices:



o. Gastrointestinal ulcers or other gastrointestinal bleeding:



p. Biliary diversion:



q. Metabolic acidosis:



r. Edema:



s. Hepatic encephalopathy:



t. Any other evidence of chronic liver disease:



u. Currently active inflammatory bowel disease:



v. Short bowel syndrome:



w. Small intestine resection:



x. Renal dysfunction with creatinine clearance < 90 mL/min/m²:



v. Hemophilia (bleeding disorder):



z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:

aa. Endocrine disease (hormonal abnormality):	()	ax. Dermatologic disorders:
,	(1)	ay. Myopathy: (₁)
ab. Asthma:	(1)	az. Myositis:
ac. Hepatocellular carcinoma:		ba. Major depression:
ad. Other malignancy (cancer):		bb. Schizophrenia: (₁)
A di constituent di constituent		bc. Bipolar disorder: (1)
ae. Active malignant disease requiring chemotherapy or radiation within		bd. Obsessive compulsive disorder: (1)
past year:		be. Severe anxiety or personality disorder: (1)
af. Human immunodeficiency virus (HIV):		bf. Substance abuse:
ag. Peripheral neuropathy:	<u>(</u>)	bg. None of the above:
ah. Active seizure disorder or epilepsy	y: (₁)	20. Has the patient ever had bariatric surgery for any of the following (check all that apply)
ai. Drug allergies:	(₁)	a. Stapling or banding of the stomach:
aj. Hypothyroidism:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	b. Jejunoileal (or other intestinal)
ak. Hypertension:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	bypass:
al. Cerebrovascular disease:	(1)	(E)vig)—
am. Hyperlipidemia (high cholesterol high triglycerides):	•	c. Biliopancreatic diversion:
an. Pancreatitis:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	d. Other bariatric surgery (specify):
ao. Cholelithiasis:	(1)	C 1
ap. Coronary artery disease:		
aq. Congestive heart failure:		e. None of the above: (1)
ar. Myocardial infarction:	(₁)	21. Is the patient currently undergoing evaluation for bariatric surgery: Yes No
as. Unstable arrhythmias:	(1)	
at. Elevated uric acid such as gout:	(₁)	22. Has the patient received total parenteral nutrition (TPN) in the past year:
au. Kidney disease:	(₁)	$\left(\begin{array}{c} \text{Yes} \\ 1 \end{array}\right)$ [Fig. $\left(\begin{array}{c} \text{No} \\ 2 \end{array}\right)$
av. Polycystic ovary syndrome:	(₁)	
aw. Sleep apnea:	(1)	

- 23. Organ, limb, or bone marrow transplant
 - **a.** Has the patient ever received a liver transplant:

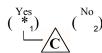


b. Has the patient ever received any other organ, limb, or bone marrow transplant:

Yes		No			
(1)	(2)		

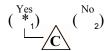
E. Drugs historically associated with NAFLD

- **24.** Has the patient used any tetracyclines, salicylates, valproic acid or other known hepatotoxins in the past year *(check all that apply)*
 - **a.** Amiodarone (Pacerone):
 - **b.** Demeclocycline (Declomycin): (1)
 - **c.** Divalproex (Depakote):
 - **d.** Doxycycline (Monodox):
 - **e.** Isonicotinylhydrazine (INH, Isoniazid, Tubizid): (1)
 - **f.** Isotretinoin (Accutane, Amnesteem, Clarvis, or Sotret):
 - **g.** Methotrexate (Rheumatrex):
 - h. Minocycline (Dynacin, Minocin):
 - i. Oxytetracycline (Terramycin):
 - j. Tetracycline (Achromycin):
 - **k.** Valproate sodium (Depacon): (1)
 - **1.** Valproic acid (Depakene):
 - **m.** Other known hepatotoxin (specify):
 - **n.** None of the above:
- 25. Were any of the items in 24a-m checked:



*Caution: Use of any of these drugs for more than 2 consecutive weeks in the past year or in the 90 days prior to liver biopsy is exclusionary.

- **26.** Has the patient taken any systemic glucocorticoids in the past year *(check all that apply)*
 - **a.** Betamethasone sodium (Celestone): $\binom{1}{1}$
 - **b.** Cortisol: (1)
 - c. Cortisone:
 - **d.** Dexamethasone (Decadron): (1)
 - **e.** Hydrocortisone (Hydrocortone): (₁)
 - **f.** Methylprednisolone (Solu-Medrol): (1)
 - **g.** Prednisolone (Prelone):
 - **h.** Prednisone:
 - i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort):
 - **j.** Other, (specify):
 - **k.** Other, (specify):
 - **I.** None of the above:
- **27.** Were any of the items 26a-k checked:



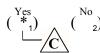
*Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past year is exclusionary.

28.	Has the patient taken any anabolic
	steroids or tamoxifen in the past year
	(check all that apply)

a.	Boldenone	undecylenate	(Equipoise):	(,)
		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	(-1r).	•	1/

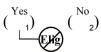
k. Other, (specify):
$$\begin{pmatrix} 1 \end{pmatrix}$$

29. Were any of the items 28a-l checked:



*Caution: Use of anabolic steroids or tamoxifen for more than 2 consecutive weeks in the past year is exclusionary.

30. Does the patient have a known intolerance to cysteamine bitartrate:



F. Use of antidiabetic drugs

31. Has the patient used any antidiabetic medications in the past 6 months:

Y	es	1	No
(1)	(2)
		·	1
		32. —	

a.	Acarbose	(Precose):	(.	1)	
----	----------	------------	-----	----	--

G. Use of supplements, vitamins, and other drugs

32. Has the patient taken any of the following supplements/drugs in the past 6 months:

(Ye	es 1)		(N	lo 2
	ſ	34.		J

(If yes, check all that apply)

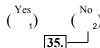
- a. Betaine (Cystadone):
- **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler):
- c. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol):
- **d.** S-Adenylmethionine (SAM-e):
- e. Milk thistle:
- f. Probiotics: 1)
- g. Gemfibrozil (Gen-Fibro, Lopid): 1)
- **h.** Vitamin E:
- ₁) **i.** Other (specify):

specify

33. Were any of the medications/supplements checked in items 32a-i initiated after the screening liver biopsy being used for CyNCh:



34. Has the patient taken any vitamins in the past 6 months:

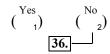


(If yes, check all that apply)

- a. Vitamin A:
- **b.** Vitamin B (any type):
- c. Vitamin C:
- d. Vitamin D:
- e. Vitamin E:
- **f.** Multivitamin:
- g. Other, (specify):

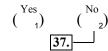
H. Use of statins, fibrates, and antiobesity drugs

35. Has the patient taken any lipid lowering medications in the past 6 months:



- a. Atorvastatin (Lipitor):
- **b.** Colestipol hydrochloride (Colestid):
- **c.** Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate):
- **d.** Fenofibrate (Tricor):
- e. Fluvastatin sodium (Lescol):
- **f.** Lovastatin (Mevacor):
- g. Nicotinic acid (Niaspan):
- **h.** Pravastatin sodium (Pravachol):
- i. Rosuvastatin (Crestor):
- **j.** Simvastatin (Zocor):
- **k.** Other, (specify):

36. Has the patient taken any antiobesity medications in the past 6 months:

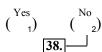


(If yes, check all that apply)

- **a.** Dexfenfluramine hydrochloride (Redux): (1)
- **b.** Fenfluramine hydrochloride (Pondimin):
- c. Methamphetamine hydrochloride (Desoxyn, Gradumet):
- **d.** Orlistat prescription (Xenical):
- e. Orlistat (over-the-counter Alli):
- **f.** Phendimetrazine tartrate (Adipost, Bontril):
- g. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
- **h.** Other, (specify):
- i. Other, (specify):

I. Use of other medications and supplements

37. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 6 months:



(If yes, check all that apply)

- **a.** Acetaminophen (Tylenol):
- **b.** Aspirin 325 mg: (1)
- **c.** Ibuprofen (Advil, Motrin): (1)
- **d.** Naproxen (Aleve, Naprosyn):
- e. Other, (specify):
- f. Other, (specify):

38. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 6 months:

Yes		No		
(1)	(2)	
	3	39. —	J	

- **a.** Cimetidine (Tagamet):
- **b.** Esomeprazole magnesium (Nexium): (1)
- c. Famotidine (Pepcid):
- **d.** Lansoprazole (Prevacid):
- e. Nizatidine (Axid):
- **f.** Omeprazole (Prilosec):
- **g.** Ranitidine (Zantac):
- **h.** Ranitidine bismuth citrate (Tritec):
- i. Antacids, (specify):
- **j.** Other, (specify):
- **k.** Other, (specify):

39. Has the patient taken any cardiovascular/antihypertensive medications in the past 6 months:

Y	es \	, N	No \
(1)	(2)
	4	0.	J

(If yes, check all that apply)

a.	Amlodipine besylate (Norvasc): (1.)
a.	Amlodipine besylate (Norvasc): (1.)

- **b.** Aspirin 81 mg:
- c. Atenolol (Tenormin):
- **d.** Benazepril (Lotensin):
- e. Captopril (Capoten):
- **f.** Clonidine (Catapres):
- g. Digoxin (Lanoxin):
- **h.** Diltiazem (Cardizem):
- i. Doxazosin (Cardura):
- j. Enalapril (Vasotec):
- k. Felodipine (Plendil):
- **1.** Furosemide (Lasix):
- **m.** Hydrochlorothiazide (Esidrix, HydroDIURIL): $\begin{pmatrix} & & & \\ & & & \end{pmatrix}$
- **n.** Hydrochlorothiazide + triamterene (Dyazide): (1)
- o. Lisinopril (Prinivil, Zestril): (1)
- **p.** Losartan potassium (Cozaar): (
- **q.** Losartan potassium with hydrochlorothiazide (Hyzaar): (1)
- **r.** Metoprolol (Lopressor): (1)
- s. Nifedipine (Adalat, Procardia): $\binom{1}{1}$
- t. Perhexiline maleate: (1)
- u. Propranolol (Inderal):

 ()
- v. Quinapril (Accupril):
- w. Terazosin (Hytrin): (1)
 x. Timolol maleate (Blocadren): (1)
- y. Valsartan (Diovan):
- z. Verapamil (Calan):
- **aa.** Other, (specify):
- **ab.** Other, (specify):

40. Has the patient taken any allergy or asthma medications in the past 6 months that have not already been reported on this form:

Yes	(No
\ I/	41.

(If yes, check all that apply)

- **a.** Albuterol: (1)
- **b.** Beclomethasone dipropionate (Beclovent, Vanceril):
- **c.** Budesonide (Pulmicort, Rhinocort): (1)
- **d.** Fluticasone propionate (Flonase, Flovent):
- e. Loratadine (Claritin):
- **f.** Mometasone furoate (Nasonex):
- g. Triamcinolone acetonide (Azmacort,
 Nasacort):
- **h.** Other, (specify):
- i. Other, (specify):
- **41.** Has the patient taken any antipsychotic or antidepressant medications in the past 6 months:

Yes (1)	$\binom{No}{2}$
	42.

- **a.** Aripipazole (Abilify):
- **b.** Buporpion (Wellbutrin): (1)
- **c.** Clomipramine (Anafranil): (1)
- d. Escitalopram (Lexapro): (1)e. Fluoxetine (Prozac): (1)
- f. Fluvoxamine (Luvox):
- g. Lithium (Eskalith, Lithobid):
- **h.** Quetiapine (Seroquel):
- i. Risperidone (Risperdal):
- j. Sertraline (Zoloft):
- **k.** Other (specify): $\begin{pmatrix} 1 \end{pmatrix}$

42. Has the patient taken any supplements in the past 6 months that have not already been reported on this form:

Y	es \	(No \
(1)	(2)
	4	43. —	

1)

1)

(If yes, check all that apply)

a. Alpha-lipoic acid:	(
b. Beta-carotene:	(

- c. Calcium (any form):
- d. Carnitine (any form):e. Chondroitin (any form):
- **f.** Cod liver oil:
- g. Coenzyme Q:
- **h.** Dichloroacetate: (1)
- i. Echinacea:
- j. Fish oil (any form):

 k. Flax seed oil:
- **k.** Flax seed oil: (₁) **l.** Garlic: (.)
- m. Ginkgo biloba:
- **n.** Glucosamine (any form):
- o. Lecithin:
- **p.** Magnesium: (1)
- **q.** N-acetyl-cysteine: (1)
- r. Potassium (any form):
- s. Saw palmetto:
- t. Selenium: (1)
- **u.** St. John's Wort: (1)
- v. Taurine: (1)
 w. Zinc picolinate: (1)
- **x.** Other, (specify):
- \mathbf{y} . Other, (specify): $\begin{pmatrix} 1 \end{pmatrix}$

43. Has patient taken any of the following medications in the past 6 months:

$\binom{\text{Yes}}{1}$	$\binom{\text{No}}{2}$
	44.

(If yes, check all that apply)

- **a.** Isotretinoin (Accutane):
- **b.** Levonorgestrel (Norplant):
- **c.** Levothyroxine (Levoxyl, Synthroid): (
- **d.** Liothyronine (Cytomel):
- e. Oral contraceptives:
- **f.** Penicillamine (Cuprimine, Depen): (1)
- **g.** Trientine hydrochloride (Syprine): (1)
- **h.** Other, (specify):
- i. Other, (specify):
- **j.** Other, (specify):
- **k.** Other, (specify):
- l. Other, (specify):
- J. Administrative information
- **44.** Study Physician PIN:
- **45.** Study Physician signature:
- **46.** Clinical Coordinator PIN:
- **47.** Clinical Coordinator signature:
- _____
- **48.** Date form reviewed:

mon

day

year

CyNCh

BP - Blood Processing for Plasma and Serum

Purpose: Document collection of fasting blood for separation of plasma and serum.

When: Visits s, f12, f24, f36, f52 and f76.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of blood.

Instructions: Label tubes of blood using MACO labels specific for the patient and visit; these labels are generated by the clinical center upon registration (screening visit labels) or after enrollment (follow-up visit labels). Attach duplicate blood tube labels in items 11 and 13. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Label 2.0 mL cryovials with numbered patient-specific plasma (blue-top) and serum (red-top) cryovial labels provided by the DCC. Affix plasma aliquot #00 label and serum aliquot #00 label to this form in item 18. If blood was previously collected for the NAFLD Database 2 and is being used for CyNCh, transcribe the data from the Database 2 BP form, including the cryovial label information, and attach that form to the CyNCh BP form. If blood is not collected at the screening visit, the child is not eligible for CyNCh unless previously collected samples are available.

For plasma: Fill <u>one</u> 10 mL green top heparin tube with blood. Process blood for plasma within 30 minutes according to procedures specified in the CyNCh SOP I, section 6. After separation, prepare up to 10 aliquots of plasma: pipette 0.5 mL of plasma to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of plasma at -70 C.

For serum: Fill <u>two</u> 10 mL SST red-gray top tubes with blood. Process blood for serum within two hours according to procedures specified in the CyNCh SOP I, section 6. After separation, prepare up to 20 aliquots of serum: pipette 0.5 mL of serum to each prelabeled 2.0 mL cryovial. Immediately freeze labeled aliquots of serum at -70 C

NOTE: Immediately upon completion of plasma and serum aliquot preparation, destroy any leftover cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be able to be determined.

A. Center, patient and visit	iaentiii	catioi	1	
1. Center code:				
2. Patient ID:				
3. Patient code:				
4. Date of visit:				
day	mon		y	ear
5. Visit code:				
6. Form & revision:		_b_	_p_	_2_
7. Study:		C	yNCł	n_8_

B. Processing whole blood

Plasma and serum aliquots are to be separated from blood per instructions in the SOP I. Draw fasting blood in the morning.

8. Was participant fasting for at least 8 hours* prior to blood draw:

 $\begin{pmatrix} \text{Yes} & \text{No} \\ 1 & \end{pmatrix} & \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$ *A 12-hour fast is preferred, but will accept non-fasting samples.

a. Was blood collected for the NIDDK Biosample Repository:

Yes	(1.
Yes, previously collected for NAFL	D	
Database 2	(*	2
No, (specify):	(†	3
	23.	

specify reason

*If using blood collected for NAFLD Database 2, transcribe Database 2 BP form to this form and attach a copy.

†Blood collection is required at the screening visit unless samples previously collected for Database 2 are being used; do not key form. If patient did not come to clinic for follow-up visit, complete the MV form instead of the BP form.

Patient ID:		

	Patient ID:		
9. Date and time of blood draw	C. Aliquots for plasma and serum Pinetta 0.5 mL of plasma into each of un to ten 2.0		
a. Date:	Pipette 0.5 mL of plasma into each of up to ten 2. mL pre-labeled cryovials and pipette 0.5 mL of		
day mon year b. Time:	serum into each of up to 20 2.0 mL pre-labeled cryovials.		
hour minute (1) (2	15. Date and time of separation into plasma and serum aliquots		
10. Number of heparin (green-top) tubes:	a. Date: day mon year		
11. Affix matching heparin tube MACO label	b. Time of plasma separation:		
(only key NASH ID): CyNCh Form BP,	hour iminute (1) (2)		
BP Plasma.	c. Time of serum separation:		
Pt: 9999, xyz Visit vvv	hour minute am pm		
Date:	16. Number of aliquots for plasma:		
12. Number of SST serum separator	17. Number of aliquots for serum:		
(red-gray top) tubes: 13. Attach duplicate SST serum separator	18. Attach duplicate cryovial labels (use aliquot #00 labels which are located in the first row of labels in the set):		
tube labels (only key NASH ID): CyNCh Form BP, Serum 1 Pt: 9999, xyz	Serum aliquot #00 label Plasma aliquot #00 label		
Visit: vvv BP			
Date:			
CyNCh Form BP, Serum 2			
Pt: 9999, xyz Visit: vvv	19. Technician		

BPDate:

14. Phlebotomist:

print name

print name

D. Freezing aliquots

Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK Biosample Repository at Fisher BioServices.

20. Date and time cryovials frozen in -70°C or -20°C

a Date

i. Date:			
	day	mon	vear

h Time:

11me:			
hour	minute	(₁)	(pm 2

- **21.** Number of cryovials frozen: _____
- **22.** Technician:

print name

E. Administrative information

- **23.** Clinical Coordinator PIN: ____ ___
- **24.** Clinical Coordinator signature:

25. Date form reviewed:

day mon year

CG - Genetic Consent and Blood Collection Documentation

Purpose: To document options selected for use of blood samples for genetic research and the collection of whole blood for DNA extraction and banking at the NIDDK Genetics Repository at Rutgers University.

When: Screening visit s or as needed during follow-up due to a low yield (less than 50 µg) of DNA (during follow-up, use the visit code of the follow-up visit that is open).

By whom: Study Physician, Clinical Coordinator and laboratory personnel responsible for collection of blood.

Instructions: Complete this form based on the consent documents signed by the patient. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG form. If the patient consents, (1) Apply MACO labels specific for the patient and visit to the EDTA vacutainer tubes; these labels are generated by the clinical center upon registration (screening labels). Affix duplicate tube label in item 18. (2) Fill two 10 mL EDTA vacutainer tubes with whole blood (see SOP I, section 6). (3) Pack the whole blood tubes in the specimen shippers supplied by the NIDDK Genetics Repository. Use the preprinted Federal Express shipping label, marked for Priority Overnight Delivery, to ship whole blood at ambient room temperature to the NIDDK Genetics Repository Monday-Friday on the same day it is collected.

Α.	Center.	natient	and	visit	identific	ation
A.	Cuitti,	patient	anu	VISIL	Iuciitiic	auvn

1.	Center ID:		 	

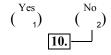
2. Patient ID:	
Z. Patient ID.	

4.	Date	form	compl	leted
----	------	------	-------	-------

6. Form & revision:

day	mon	year

8. Has a sufficient yield of DNA (≥100 micrograms) been banked at the NIDDK Genetics Repository for this participant in a previous NASH CRN study:

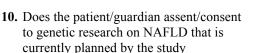


<u>c g 1</u>

9. For which study was it collected *(check all that apply):*

a. Database	(.)
. Butuouse	\ 1	,

	 00,			17
		. c		
		specify		
		1 5		



$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

11. Does the patient/guardian assent/consent to future genetic research on NAFLD by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

20. –

12. Does the patient/guardian assent/consent to future genetic research not related to NAFLD by this study or other study investigators:

$$\binom{\text{Yes}}{1}$$
 $\binom{\text{No}}{2}$

Patient ID:	 	

13. Other information related to consent for genetic research that clinic staff feel needs to be keyed to the study database (e.g., if your genetic consent had other options that are not covered by the 3 categories of use of samples specified above):

14. In your judgment, has the patient consented to collection of blood for DNA

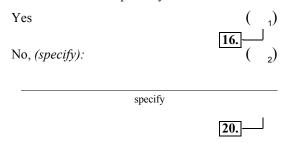
banking (this question is asked in recognition that not all IRBs will have approved consent statements that include language that can be mapped into the questions in items 10 through 12; a response of "No" to this question (item 14) means that blood should NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):



C. Specimen for Genetics Repository

Attach ID labels to two 10 mL EDTA tubes and fill each with blood; invert each tube gently 6 times to mix blood with additives; keep tubes at room temperature until the same day shipment to the NIDDK Genetics Repository.

15. Was blood collected today for the NIDDK Genetics Repository:



- 16. Date and time of blood draw
- **17.** Number of 10 mL EDTA tubes:

18. Attach form copy of tube label:

CyNCh Form CG
Pt: ccc- 9999, xyz
Gender
Age, yrs.: XX

19. Phlebotomist:

print name

D. Administrative information

- **20.** Study Physician PIN:
- 21. Study Physician signature:
- **22.** Clinical Coordinator PIN:
- **23.** Clinical Coordinator signature:
- **24.** Date form reviewed:

day	mon	year

CO - Closeout Form

Purpose: To close out a patient's participation in CyNCh and document the patient's consent to join or re-enter the NAFLD Database 2 study.

When: At f76 visit or at the close of the f76 window.

Respondent: Clinical coordinator.

Instructions: Complete this form for each patient randomized in CyNCh at the f76 visit or at the close of the f76 window. Determine if the patient now wants to re-enter or join the NAFLD Database 2. Schedule the patient for a NAFLD Database 2 follow-up visit approximately 12 months from this visit.

(1) Patients previously enrolled in the NAFLD Database 2: consult the NAFLD Database 2 visit schedule generated at NAFLD parallement and use the visit window that is open in 12 months

ated at NAFLD enrollment and use the visit window that is open in 12 months.

(2) Patients NOT previously enrolled in the NAFLD Database 2: if patient is willing to join the NAFLD Database 2, a visit schedule will be generated upon keying this form. Schedule the participant approximately 12 months from their CyNCh f76 visit for their t144 NAFLD Database 2 follow-up visit.

A. Center, patient and visit identification

- 1. Center ID: ____ ____
- **2.** Patient ID: ____ ___ ____
- **3.** Patient code: _____ ____
- **4.** Date of visit:

dav

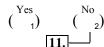
5. Visit code: __f__7__6

mon

- **6.** Form & revision: __c__ o__ 1__
- 7. Study: CyNCh <u>8</u>

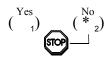
B. Database participation

8. Does the patient/parent wish to re-enter or join the NAFLD Database 2:



vear

Has the patient/parent signed the latest version of the NAFLD Database 2 informed consent:



* Patient/parent must sign the informed consent

10. Was the patient enrolled in the NAFLD Database 2 previously:

 $\binom{\text{Yes}}{*}$ $\binom{\text{No}}{+}$

* Schedule the patient's next NAFLD Database 2 follow-up visit approximately 12 months from the date in item 4. Consult the patient's NAFLD Database 2 visit schedule and use the NAFLD Database 2 visit open on that date.

+ Data system will generate a visit window schedule assigning the CyNCh randomization date as the NAFLD Database 2 enrollment date. Schedule the patient approximately 12 months from the date in item 4 for their t144 NAFLD Database 2 followup visit.

C. Administrative information

- **11.** Clinical Coordinator PIN: ____ ___
- **12.** Clinical Coordinator signature:

13. Date form reviewed:

day	mon	year

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.

When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee.

By whom: Data Coordinating Center staff.

Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

	A. Clinic, patient and visit identification 1. Center ID
_	2. Patient ID
	3. Patient code
///	4. Date of central reading
	5. Visit code
<u>c r 2</u>	6. Form and revision
	7. Study: 6 =Database 2; 7 =FLINT; 8 =CyNCh
///	8. Date of biopsy
	B. Slide sequence number9. Sequence number for a. H & E stained slide
<u> </u>	b. Masson's trichrome stained slide
<u> </u>	c. Iron stained slide
	C. Adequacy of biopsy 10. Biopsy length (mm)
	11. Tissue adequate: 0 =No → Request original slides from submitting clinic; 1 =Yes
	12. Followup with clinic (Specify):
D. Hi H & E stain 13. Steatosis (assume macro, e.g., large and small drople a. Grade: 0=<5%; 1=5-33%; 2=34-66%; 3=>66%	estology et)

... c. Type of macrovesicular steatosis: **0**=Predominantly large droplet; **1**=Mixed large and small droplet;

_____ b. Location: **0**=Zone 3 (central); **1**=Zone 1 (periportal); **2**=Azonal; **3**=Panacinar

d. Microvesicular steatosis, contiguous patches: **0**=Absent; **1**=Present

2=Predominantly small droplet

 Patient ID	D. Histology (cont'd)
14. Inflammation	
	ılar inflammation: combines mononuclear, fat granulomas, and pmn foci:
	der 20x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag
	has seen: 0=No; 1=Yes
	ilomas seen: 0=No; 1=Yes
	al, chronic inflammation: 0 =None; 1 =Mild; 2 =More than mild
di i ililodili oi poi	, • • 1
15. Liver cell injury	
	None → GOTO Item 15d; 1=Few; 2=Many
	ing present: 0=No; 1=Yes
c. Classical ballo	on cells present: 0 =No; 1 =Yes
d. Acidophil bodi	es: 0=Rare/absent; 1=Many
e. Pigmented mad	rophages (Kupffer cells): 0 =Rare/absent; 1 =Many
 f. Megamitochon	dria: 0 =Rare/absent; 1 =Many
 16. Mallory-Denk bo	lies: 0=Rare/absent; 1=Many
 17. Glycogen nuclei:	0=Rare/absent; 1=Present in patches
10 01 ' 01	0 N
	epatocytes: 0 =Not present; 1 =Focal, involving less than 50% of the hepatocytes; 2 =Diffuse,
involving greater	than or equal to 50% of the hepatocytes
19. Masson's trichro	ma atain
	0=None → GOTO Item 20; 1a=Mild, zone 3 perisinusoidal (requires trichrome);
	, zone 3, perisinusoidal (does not require trichrome); 1c=Portal/periportal only;
	periportal, any combination; 3=Bridging; 4=Cirrhosis
	fibrosis grade: 0 =No perisinusoidal fibrosis present; 1 =Perisinusoidal fibrosis present that
	sson stain to identify; 2 =Perisinusoidal fibrosis present that is visible on the H&E stain
	cation of fibrosis: 0 =More predominance around or between portal areas; 1 =No portal or
	minance; 2=More predominance around/between central veins
•	
20. Iron stain	
a. Hepatocellular	iron grade: 0 =Absent or barely discernible, 40x → GOTO item 20c ;
	ernable granules, 20x; 2 =Discrete granules resolved, 10x; 3 =Discrete granules resolved, 4x;
	ible by naked eye
	iron distribution: 0 =Periportal; 1 =Periportal and midzonal; 2 =Panacinar; 3 =Zone 3 or azonal
	llar iron grade: 0=None → GOTO item 21; 1=Mild; 2=More than mild
 	alar iron distribution: 0 =Large vessel endothelium only; 1 =Portal/fibrosis bands only, but
more than jus	t in large vessel endothelium; 2 =Intraparenchymal only; 3 =Both portal and intraparenchymal
21 In this startahama	itie 2 00 - Net NAELD. 0 - NAELD met NACH. 1 - Chemicione/hemdenline/indeterminete. 7 - ne
	itis? 99=Not NAFLD; 0=NAFLD, not NASH; 1a=Suspicious/borderline/indeterminate: Zone
5 pattern, 10–Sus	picious/borderline/indeterminate: Zone 1, periportal pattern; 2=Yes, definite
22 Is cirrhosis presen	t? 0 =No → GOTO item 25 ; 1 =Yes
 22. Is cirrilosis preser	1: 0 100 • GOTO Rem 25, 1 105
23. Is this cryptogenie	cirrhosis: 0=No → GOTO item 25; 1=Yes
24. Features suggestiv	re of steatohepatitis etiology for cryptogenic cirrhosis:
	podies (rule out cholate stasis): 0 =Absent; 1 =Present
	fibrosis away from septa: 0 =Absent; 1 =Present
c. Hepatocyte bal	ooning: 0=Absent; 1=Present
	dria: 0 =Absent; 1 =Present
 e. Other notable f	indings: 0=Absent; 1=Present; Specify:
25 Other comments:	

CyNCh

DD – Drug Dispensing Documentation

Purpose: To document dose of CyNCh trial study drug requested for dispensing.

When: Visits f04, f12, f24, and f36. Use visit code "n" if a change in the dosage of study drug occurs at a time other than a study visit or to dispense drug outside of a study visit.

Administered by: Study Physician or Clinical Coordinator.

Instructions: This form will be used to document the dosage the patient is currently taking and the dosage prescribed at this visit. CyNCh study drug will be taken orally in the morning and in the evening 30 minutes prior to meals. Children should be instructed to take 75 mg capsules according to their weight group at randomization:

≤65 kg at baseline	4 capsules twice daily	600 mg/day
>65-80 kg at baseline	5 capsules twice daily	750 mg/day
>80 kg at baseline	6 capsules twice daily	900 mg/day

IMPORTANT:

This form **must be entered into the data system** to obtain drug bottle number(s) for dispensing to the participant. Study drug will be dispensed in bottles containing 150 capsules of 75 mg strength.

Unless the child did not tolerate the prescribed dosage, study drug should be dispensed as specified below:

Weight group	Visit	Numb Bottle	er of s/capsules	Comments
≤65 kg at baseline	f04	4	600	8 week supply + 2.7 weeks
	f12	6	900	12 week supply + 4.1 weeks
	f24	6	900	12 week supply + 4.1 weeks
	f36	7	1,050	16 week supply $+$ 2.8 weeks
>65 kg - ≤80 kg at baseline	f04	5	750	8 week supply + 2.7 weeks
	f12	7	1,050	12 week supply + 3 weeks
	f24	7	1,050	12 week supply + 3 weeks
	f36	9	1,350	16 week supply $+3.3$ weeks
>80 kg at baseline	f04	6	900	8 week supply + 2.7 weeks
<u> </u>	f12	8	1,200	12 week supply + 2.3 weeks
	f24	8	1,200	12 week supply + 2.3 weeks
	f36	11	1,650	16 week supply + 3.6 weeks

A	Center.	patient.	and	visit	idei	ntificati	Λn

1.	Center ID:	-				
2.	Patient ID:		· 			
3.	Patient code:					
4.	Visit date (date this)	form is	initiatea	<i>!</i>):		
	<u> </u>					
	day	mon		yea	ar	
5.	Visit code:					
6.	Form & revision:		<u>d</u>	<u>d</u>	_1_	

Patient ID:		

B. Study drug dispensing

8. Which weight group was the patient assigned to at randomization *(check only one)*:

 \leq 65 kg at baseline (600 mg/day) (1)

 $>65 \text{ kg} - \leq 80 \text{ kg}$ at baseline (750 mg/day) ($_2$)

>80 kg at baseline (900 mg/day) ($_3$

9. Is the patient currently taking the CyNCh study drug at the dose prescribed according to their weight group at randomization

Yes	No		
(1)	(2)		
11.			

10. How many capsules per day has the patient been taking since the last study visit:

(00-11)

1)

4)

If the patient is not taking study drug, enter "00" and skip to 13.

11. How is the patient taking the CyNCh study drug *(check only one)*:

Swallowing the capsules (

Sprinkling the capsule contents into food (2)

Swallowing some and sprinkling some (3)

Other, (specify):

12. Was the dose tolerated by the patient *(check only one)*:

Yes (1)

No, patient experienced side effects and will not take the dose prescribed at randomization (* 2)

No, patient experienced side effects and the medication was stopped (* 3)

- * If patient experienced severe and unanticipated side effects, complete the SR form.
- **13.** The prescribed dose of study drug at this visit will be:
 - **a.** Number of capsules to be taken in the morning:

b. Number of capsules to be taken in the evening:

(0-6)

(0-6)

14. Number of bottle(s) of study drug required:

(00-11)

- C. Administrative information
 - **15.** Study Physician PIN:

16. Study Physician signature:

17. Clinical Coordinator PIN: _____ ___

18. Clinical Coordinator signature:

19. Date form reviewed:

day mon year

CyNCh

DR - Death Report

Purpose: To record the report of a patient's death. **When**: As soon as clinic is notified of a patient's death.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form whenever the clinical center is informed of a patient's death. Fax a copy of the Death Report (DR) form to the DCC at (410) 955-0932; Attention: Pat Belt. Also, complete an Adverse Event (AE) form and follow the instructions to report a patient's death in CyNCh.

A. Center, patient, and visit ide	entificati	ion	11. Cause of death	
1. Center ID:			(Study Physician: use whatever knowledge y have and your best medical judgment to best cho acterize the cause of death; check only one):	ou ar-
2. Patient ID:		- <u> </u>	Heart disease (1)
3. Patient code:			Stroke (2)
	<i>C</i> .: 1		Liver disease (3)
4. Date form is initiated (date of	of notice)):	Malignancy (4)
day m	non	year	Other (specify):	5)
5. Visit code:	<u>n</u>			
6. Form & revision:	d	<u>r_1</u>	specify	
7. Study:	C	yNCh 8	specify	
				`
B. Death information			Unknown (6)
8. Date of death:			C. Administrative information	
			12. Study Physician PIN:	
day n	non	year	13. Study Physician signature:	
9. Source of death report <i>(chec</i>	k all that	t apply):	13. Study I hysician signature.	
a. Patient's family:		(1		—
b. Friend:		(1	14. Clinical Coordinator PIN:	_
c. Health care provider or N staff:	ASH CR	KN (1	15. Clinical Coordinator signature:	
d. Newspaper:		(1		
e. Funeral parlor/home:		(1	16. Date form reviewed:	
f. Medical record:		(1	day mon year	_
g. Medical examiner:		(1	,	
h. Coroner:		(1		
i. Other (specify):		(1		
other sou	rce			
other sou	ırce			
10. Place of death:				
city/state/co	ountry			
city/state/co	ountry			

CyNCh

FH - Follow-up Medical History

Purpose: To collect follow-up medical history information about the patient.
When: Visits f04, f12, f24, f36, f52 and f76.
Administered by: Clinical Coordinator, reviewed by Study Physician.
Respondent: Patient or patient's parent or guardian.

Instructions: Collect information by interview and chart review.

A. Center, visit, and patien	nt identificati	ion
1. Center ID:		
2. Patient ID:		
3. Patient code:		
4. Visit date (date this for	m is initiated):
day	mon	year
5. Visit code:		
6. Form & revision:	_ <u>f</u> _	_h1_
7. Study:	C	yNCh 8
B. Interval identification		
8. Date of last Follow-up form (if this is visit f04)		
day	mon	year
9. Visit code of last Follo History form <i>(if this is</i>		
10. Has the participant had since the last visit:	a liver biops	у
* Complete the Liver E tation (SD) form	Ye: (* Biopsy Materi	1/ し 2/
	Biopsy Materi	1/ (2/
tation (SD) form	Biopsy Materi	1/ (2/

12. Has menarche occurred:		
	(Yes 1)	(No 2)

13. If sexually active, is the patient using two effective birth control methods:

Yes	(1
No	(*	2
* Remind patient to use two forms of birth control.			
Not sexually active	(3.

D. Alcohol consumption (AUDIT-C) since the last visit

14. Since the last visit, how often have you had a drink containing alcohol:

Never	()
	17.
Monthly or less	(
Two to four times a month	(2)
Two to three times a week	(3)
Four or more times a week	(,)

15. Since the last visit, how many drinks containing alcohol have you had on a typical day when you are drinking:

1 or 2	(0
3 or 4	(1)
5 or 6	(2)
7 to 9	(3)
10 or more	(4)

16. Since the last visit, how often have you had six or more drinks on one occasion:

Never	(0
Less than monthly	(.	1)
Monthly	(2)
Weekly	(3)
Daily or almost daily	(,	4)

E. R	2. Recent medical history			x. Hemophilia (bleeding disorder):	(1)	
17.	Has the patient been diagnosed with any of the following since the last visit (check	all		y. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus:	(1)	
	that apply; source of information can be interview and/or chart review)	uii		z. Endocrine disease (hormonal abnormality):	(1)	
	a. Diabetes type 1:	(1)	aa. Asthma:	(1)	
	b. Diabetes type 2:	(1)	ab. Hepatocellular carcinoma:	(1)	
	c. Hepatitis B:	(1)	ac. Other malignancy (cancer):	(1)	
	d. Hepatitis C:	(1)	ad. Human immunodeficiency virus			
	e. Autoimmune hepatitis:	(1)	(HIV):	(1)	
	f. Autoimmune cholestatic liver disorder	,	,	ae. Peripheral neuropathy:	(1)	
	(PBC or PSC):	(1)	af. Active seizure disorder or epilepsy:	(1)	
	g. Wilson's disease:	(1)	ag. Drug allergies:	(1)	
	h. Alpha-1-antitrypsin (A1AT) deficiency:	(1)	ah. Hypothyroidism:	(1)	
	i. Hemochromatosis or iron overload:	(1)	ai. Hypertension:	(1)	
	j. Drug induced liver disease:	(1)	aj. Cerebrovascular disease:	(1)	
	k. Ascites:	(1)	ak. Hyperlipidemia (high cholesterol, high triglycerides):	(1)	
	l. Gilbert's syndrome:	(1)	al. Pancreatitis:	(1)	
	m. Esophageal or gastric varices on	,		am. Cholelithiasis:	(1)	
	endoscopy:	(1)	an. Coronary artery disease:	(1)	
	n. Bleeding from varices:	(1)	ao. Congestive heart failure:	(1)	
	 Gastrointestinal ulcers or other gastrointestinal bleeding: 	(1)	ap. Myocardial infarction:	(1)	
	p. Biliary diversion:	(1)	aq. Unstable arrhythmias:	(1)	
	q. Metabolic acidosis:	(1)	ar. Elevated uric acid such as gout:	(1)	
	r. Edema:	(1)	as. Kidney disease:	(1)	
	s. Hepatic encephalopathy:	(1)	at. Polycystic ovary syndrome:	(1)	
	t. Any other chronic liver disease:	(1)	au. Sleep apnea:	(1)	
	u. Inflammatory bowel disease:	(1)	av. Dermatologic disorders:	(1)	
	v. Short bowel syndrome:	(1)	aw. Myopathy:	(1)	
	w. Small intestine resection:	(1)	ax. Myositis:	(1)	
			12	ay. Major depression:	(1)	
				az. Schizophrenia:	(1)	
				ba. Bipolar disorder:	(1)	
				bb. Obsessive compulsive disorder:	(1)	
				bc. Severe anxiety or personality disorder:	(1)	
				bd. Substance abuse:	(1)	
				be. None of the above:	(1)	

NΙο

18.	Since the last visit, has the patient had
	bariatric surgery (check all that apply)

a.	Stapling	or banding	of the stomach:	(1)	į
----	----------	------------	-----------------	---	----	---

e.	None of the above:	(1)

F. Drugs historically associated with NAFLD

19. Since the last visit, has the patient used any of the following:

Yes	No
(1)	(2)
	20.

(If yes, check all that apply)

a.	Amiodarone (Pacerone):	(1.

m. Other known hepatotoxin (specify):
$$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$$

20. Since the last visit, has the patient taken any systemic glucocorticoids:

$\binom{1}{1}$	(2)
(If yes, check all that apply)	1.	J
a. Betamethasone sodium (Celestone):	(1)
b. Cortisol:	(1)
c. Cortisone:	(1)
d. Dexamethasone (Decadron):	(1)
e. Hydrocortisone (Hydrocortone):	(1)
f. Methylprednisolone (Solu-Medrol):	(1)
g. Prednisolone (Prelone):	(1)
h. Prednisone:	(1)
i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort):	(1)
i. Other, (specify):	(1)

21. Since the last visit, has the patient taken any anabolic steroids or tamoxifen:

$$\binom{\text{Yes}}{1} \binom{\text{No}}{2}$$

a.	Boldenone	undecylenate	(Equipoise):	(1)
----	-----------	--------------	--------------	---	----

c. Methandrostenolone (Dianabol):
$$\begin{pmatrix} & & \\ & & \end{pmatrix}$$

G. Use of antidiabetic drugs

22. Since the last visit, has the patient used any antidiabetic medications:

Yes	, No
$\begin{pmatrix} 1 \end{pmatrix}$	(₂)
	23.

(If yes, check all that apply)

a. Acarbose (Precose):	(1)	

- **b.** Acetohexamide (Dymelor):
- **c.** Chlorpropamide (Diabinese): (1)
- **d.** Exenatide (Byetta, Bydureon): (1)
- e. Glimepiride (Amaryl):
- **f.** Glipizide (Glucotrol): (1)
- **g.** Glyburide (Micronase): $\binom{1}{1}$
- **h.** Insulin: (₁)
- i. Metformin (Glucophage): (1)j. Miglitol (Glycet): (1)
- **k.** Nateglinide (Starlix):
- I. Pioglitazone (Actos):
- **m.** Repaglinide (Prandin): (1)
- **n.** Rosiglitazone (Avandia):
- o. Tolazamide (Tolinase):
- **p.** Tolbutamide (Orinase): (1)
- **q.** Other, (specify):

H. Use of supplements, vitamins, and other drugs

23. Since the last visit, has the patient taken any of the following supplements/drugs:

Yes)	(No
(1)	24.	

(If yes, check all that apply)

- **a.** Betaine (Cystadone):
- **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
- c. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
- **d.** S-Adenylmethionine (SAM-e):
- e. Milk thistle:
- **f.** Probiotics: (1)
- **g.** Gemfibrozil (Gen-Fibro, Lopid):
- **h.** Vitamin E:
- i. Vitamin A:
- **j.** Vitamin B (any type):
- **k.** Vitamin C: (₁)
- I. Vitamin D:
- m. Multivitamin:
- **n.** Other (specify): $\begin{pmatrix} 1 \end{pmatrix}$

specify

I. Use of statins, fibrates, and antiobesity drugs

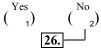
24. Since the last visit, has the patient taken any lipid lowering medications:

Yes	No .	
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	25.	

(If yes, check all that apply)

a. Atorvastatin (Lipitor):	(1
b. Colestipol hydrochloride (Colestid):	(1
c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate):	(1.
d. Fenofibrate (Tricor):	(1.
e. Fluvastatin sodium (Lescol):	(1.
f. Lovastatin (Mevacor):	(1
g. Nicotinic acid (Niaspan):	(1.
h. Pravastatin sodium (Pravachol):	(1.
i. Rosuvastatin (Crestor):	(1,

25. Since the last visit, has the patient taken any antiobesity medications:



(If yes, check all that apply)

h. Other, (specify):

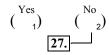
j. Simvastatin (Zocor):

k. Other, (specify):

a. Dexfenfluramine hydrochloride (Redux):	(1)
b. Fenfluramine hydrochloride (Pondimin):	(1)
c. Methamphetamine hydrochloride (Desoxyn, Gradumet):	(1)
d. Orlistat prescription (Xenical):	(1)
e. Orlistat (over-the-counter Alli):	(1)
f. Phendimetrazine tartrate (Adipost, Bontril):	(1)
g. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):	(1)

J. Use of other medications and supplements

26. Since the last visit, has the patient taken any histamine H2 receptor antagonists, antacids, or other medications:



- **a.** Cimetidine (Tagamet):
- **b.** Esomeprazole magnesium (Nexium): (1)
- **c.** Famotidine (Pepcid):
- **d.** Lansoprazole (Prevacid):
- e. Nizatidine (Axid):
- **f.** Omeprazole (Prilosec):
- g. Ranitidine (Zantac):
- **h.** Ranitidine bismuth citrate (Tritec):
- i. Antacids, (specify):
- **j.** Other, (specify):

27. Since the last visit, has the patient taken any cardiovascular/antihypertensive medications:

Yes (1)	$\binom{No}{2}$
	28.

(If yes, check all that apply)		
a. Amlodipine besylate (Norvasc):	(1)
b. Atenolol (Tenormin):	(1)
c. Benazepril (Lotensin):	(1)
d. Captopril (Capoten):	(1)
e. Clonidine (Catapres):	(1)
f. Digoxin (Lanoxin):	(1)
g. Diltiazem (Cardizem):	(1)
h. Doxazosin (Cardura):	(1)
i. Enalapril (Vasotec):	(1)
j. Felodipine (Plendil):	(1)
k. Furosemide (Lasix):	(1)
I. Hydrochlorothiazide (Esidrix, HydroDIURIL):	(1)
m. Hydrochlorothiazide + triamterene (Dyazide):	(1)
n. Lisinopril (Prinivil, Zestril):	(1)
o. Losartan potassium (Cozaar):	(1)
p. Losartan potassium with hydrochlorothiazide (Hyzaar):	(1)
q. Metoprolol (Lopressor):	(1)
r. Nifedipine (Adalat, Procardia):	(1)
s. Perhexiline maleate:	(1)
t. Propranolol (Inderal):	(1)
u. Quinapril (Accupril):	(1)
v. Terazosin (Hytrin):	(1)
w. Timolol maleate (Blocadren):	(1)
x. Valsartan (Diovan):	(1)

28. Since the last visit, has the patient taken any antipsychotic or antidepressant medications:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2)
	29.

(If yes, check all that apply)

- **a.** Aripipazole (Abilify):
- **b.** Buporpion (Wellbutrin):
- c. Clomipramine (Anafranil):
- d. Escitalopram (Lexapro):
- e. Fluoxetine (Prozac):
- **f.** Fluvoxamine (Luvox):
- **g.** Lithium (Eskalith, Lithobid):
- **h.** Quetiapine (Seroquel):
- i. Risperidone (Risperdal):
- **j.** Sertraline (Zoloft):
- **k.** Other (specify):
- K. Administrative information
- 29. Study Physician PIN:
- **30.** Study Physician signature:

32. Clinical Coordinator signature:

- **33.** Date form reviewed:

_		_
day	mon	year

y. Verapamil (Calan): **z.** Other, (specify):

CyNCh

HF - Liver Biopsy Histology Findings

Purpose: Record results of the histologic evaluation of slides from the liver biopsy for eligibility. **When**: Visit s.

By whom: Clinical Coordinator after Study Pathologist completed the Histology Worksheet (HW form).

Instructions: The Study Pathologist should complete the Histology Worksheet (HW) using the institution's H & E slide and if available, the institution's Masson's trichrome and iron slides. After completing the HW form, the Study Pathologist should give the worksheet to the Clinical Coordinator who will transcribe the data to the HF form and staple the worksheet to the HF form. If () is checked for any item, the patient is not eligible for CyNCh and the form should not be keyed. If \(\subseteq \) is checked for an item, use caution; if the Study Physician agrees with the diagnosis, the patient is ineligible for CyNCh and the form should not be keyed.

If fewer than 3 unstained slides are available for the biopsy, the institution's H & E and Masson's trichrome slides must be sent to the DCC for central pathology review. If 3 or more unstained slides are available for the biopsy, only the unstained slides need to be sent to the DCC. The Study Pathologist should forward the stained slides (if needed) and up to 10 unstained slides to the Clinical Coordinator for forwarding to the DCC.

A. Center, patient and visit identification				C. NASH evaluation (use H & E and Masson's trichrome slides only)		
1.	Center ID:					
2.	Patient ID:			11. Steatosis (assume macro, e.g., large and droplet)	nd sr	mall
			a. Grade:			
3.	Patient code:			< 5%	<u>)</u> ((₀
4	Date of visit:			5-33%	بخا	1)
4.	Date of visit.			34-66%	Ì	`
	day mor	n year		> 66%	(
	•	•		b. Location:		J,
5.	Visit code:	_S		Zone 3	((ر
				Zone 1	Ì	
6.	Form & revision:	_hf1		Azonal	(
				Panacinar	(3)
7.	Study:	CyNCh_8	<u> </u>			_
				12. Fibrosis stage (Masson's trichrome stain,)	
B. B	Siopsy information			0: None	(0
8.	Date this biopsy was performe surgical pathology report):	d (obtained fr	om	1a: Zone 3, perisinusoidal (requires trichome)	(1)
	day mor			1b: Zone 3, perisinusoidal (easily seen on H & E)	(0) (1) (2) (3) (4) (4) (4) (4) (4) (4) (4) (4) (4) (4
	day	ı year		1c: Portal/periportal only	(
9.	What slides are to be used in the evaluation (check all that apply			2: Zone 3 and periportal, any combination	(
	a. H & E:	(1)	3: Bridging	(` `
	b. Masson's trichrome:	Ì	1)	4: Cirrhosis	(
		(67
	c. Iron:	(1)			
10.	Biopsy length:					

1	2	Infla	****	ation
	.7.	1111112		amon

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

0	$\begin{pmatrix} 0 \end{pmatrix}$	
< 2 / 20x mag	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	
2-4 / 20x mag	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	
> 4 / 20x mag	$\begin{pmatrix} & & \\ & & \end{pmatrix}$	

b. Amount of portal, chronic

inflammation:		
None to minimal	(0
Mild	(1)
More than mild	(2)

14. Hepatocellular ballooning:

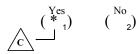
None	(0,
Few	(1.
Many	(2

15. Is steatohepatitis present:



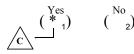
D. Exclusion of other liver disease

16. Is there evidence of primary biliary cirrhosis:



* Caution: Primary biliary cirrhosis is exclusionary

17. Is there evidence of Wilson's disease:



^{*} Caution: Wilson's disease is exclusionary

18.	Features of chronic cholestatic liver
	disease (check all that apply)

a.	Bile duct loss/infiltration/sclerosis:		(*	1)
		$\langle c \rangle$		12

b. Florid duct lesions:	((۱
DV I TOTTE GENEVI TEDICITO.	(17

e. Other (specify):	1
----------------------------	---

f. None:	(1.

19. Features of other forms of chronic liver disease (check all that apply)

a.	Vascular lesions of ALD/B-C/OVD:	())

b. Inflammation suggestive of AIH,	
HCV:	(* 1)
	/c\-

c. Pigment suggestive of HH:	(* ₁
	$\langle c \rangle$

e. Hepatocellular changes suggestive of		
HBV:	(*	1)
/0		

Granulomas suggestive of sarcoid, PBC, infection:	\c\-	(* ₁)
	/('\ -	

g. Other (specify):	(12
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^{*} Caution: Bile duct obstruction and primary sclerosing cholangitis are exclusionary

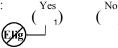
^{*} Exclusionary

E. NAFLD Activity Score

20. NAFLD activity score (NAS) (sum of items 11a, 13a, and 14)

0-8

21. Is item 20 (NAS) 3 or less:



F. Other comments

22.	Otr	ier c	omm	ients	S:			
	=							
	_							
	_							

G. Administrative information

- **23.** Study Pathologist PIN: ____ ___
- **24.** Study Pathologist signature (Pathologist does not need to sign this form if a signed HW form is attached.):
- **25.** Clinical Coordinator PIN: ____ ___
- **26.** Clinical Coordinator signature:
- 27. Date form reviewed:
- day mon year

A

LP – Symptoms of Liver Disease (Children)

Purpose: To obtain the patient's view of his/her liver disease symptoms during the CyNCh trial.

When: Visits s, f12, f24, f36, f52, and f76.

Administered by: Self-administered (age 13-17), interviewer administered (age 8-12). Clinical Coordinator must be available to answer questions and review for completeness.

Respondent: Patient, age 8 through 17. Patient age 13 or older should complete the form without help from family. Clinical Coordinator/parent should assist patient age 8-12.

Instructions: The Clinical Coordinator should complete Part A below and attach a MACO label to each of pages 2-4. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in the completion of the form, and then should complete pages 2-4. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should then complete section B below.

. Ce	nter, patient, and vi	sit ident	ificatio	on		dministrative information
1.	Center ID:					To be completed by Clinical Coordinator after urvey is completed.)
2.	Patient ID:				8.	How was the questionnaire completed:
3.	Patient code:					Self-administered by patient/parent (1)
4.	Date of visit:					10.
	day -	mon		year		Interview in English (2) Interview with translator (3)
5.	Visit code:				9.	Who was the respondent (check all that apply):
6.	Form & revision:		_1_	<u>p</u> 1		a. Patient: (1)b. Patient's mother or female
7.	Study:			CyNCh 8		guardian: (1) c. Patient's father or male guardian: (1) d. Other (specify): (1)
						specify
					10.	Clinical Coordinator a. PIN: b. Signature:
					11.	Date form reviewed:
						day mon year

Affix label	here
Patient ID:	- — —
Patient code:	
Visit code:	

Symptoms of Liver Disease

Instructions: People with liver disease may or may not have symptoms, such as pain over the liver area (under your ribs, right of your belly), feeling sick to your stomach, poor appetite (not feeling hungry), itching, or tiredness. In this questionnaire, we are trying to identify what symptoms you have, how severe they are, and how much they affect you.

(Items 1-11 are reserved for clinical center use.)

12. During the last month, how much have you been bothered by the following:

Circle one for each symptom

Degree of bother

	None at all	A little bit	Medium	Quite a bit	Extremely
a. Pain over liver (pain under ribs, right of your belly)	1	2	3	4	5
b . Nausea (sick to stomach)	1	2	3	4	5
c. Poor appetite (not hungry)	1	2	3	4	5
d . Fatigue (get tired easily)	1	2	3	4	5
e. Weight loss	1	2	3	4	5
f. Diarrhea (watery poop)	1	2	3	4	5
g. Muscle aches or cramps	1	2	3	4	5
h. Muscle weakness (feel limp)	1	2	3	4	5
i. Headaches	1	2	3	4	5
j. Easy bruising ("black and blue" marks are easy to get)	1	2	3	4	5
k. Itching	1	2	3	4	5
I. Irritability (get mad easily)	1	2	3	4	5
m. Depression/sadness	1	2	3	4	5
n. Trouble sleeping	1	2	3	4	5
o. Trouble concentrating (trouble with attention, thinking about one thing at a time)	1	2	3	4	5

Affix label here
Patient ID:
Patient code:
Visit code:

Circle one for each symptom

Degree of bother

	None at all	A little bit	Medium	Quite a bit	Extremely
p. Jaundice (yellow color to skin, eyes, etc)	1	2	3	4	5
q . Dark urine (dark pee)	1	2	3	4	5
r. Swelling of ankles	1	2	3	4	5
s. Swelling of abdomen (belly swells up)	1	2	3	4	5

13. Which of the following best describes how tired you feel and how your tiredness affects you *(choose only one)*:

Circle one

	(ircie one
	I feel normal and am not tired (If this is how you feel, please circle "1" and g	
	to item number 17 – Thank you!)	· ¹
	I feel tired some of the time, but can do what I want to do without trouble	2
	I feel tired, and do what I want but with trouble	3
	I feel tired and it keeps me from doing what I want to do	4
14.	How often are you bothered by being tired (choose only one):	
	All day, every day	. 1
	Part of the day, every day	
	At least part of several days a week	
	At least part of one day a week	
	Not as much as above	
15.	Are you tired (choose only one):	
	When you wake up in the morning	. 1
	Or does it come on with the day	
	Or does it have no time pattern	

Affix label here
Patient ID:
Patient code:
Visit code:
L

16.	Do you feel more tired the day after you exercise or have a lot of activity:
	Yes
17.	In general, how have you felt overall in the past month:
	Very good 1 Good 2 Fair 3 Poor 4 Awful 5
18.	Today's date:

Thank you for completing this questionnaire.

LR - Laboratory Results - Tests Done at Screening and Followup Visits

Purpose: To record archival and current laboratory test results for tests done during both screening and followup.

When: Visits s, f04, f12, f24, f36, f52, and f76.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. Attach copies of the laboratory reports to this form. If we is checked for any item, then the form should not be keyed.

A. Center, patient, and visit identification	12. White blood cell values
1. Center ID:	a. White blood cell count (WBC):
2. Patient ID:	$10^3 \text{ cells/} \mu L$ or $10^9 \text{ cells/} L$ If WBC < 3.5 10^3 cells/mm ³ at screening, patient is ineligible.
3. Patient code:	<u> </u>
4. Date of visit:	b. Neutrophils:
day mon year 5. Visit code:	c. Lymphocytes: cells/ μL
6. Form & revision: 1 r 1	d. Monocytes: cells/μL
7. Study: CyNCh <u>8</u>	e. Eosinophils: cells/μL
B. Hematology Required at all visits.	f. Basophils:
8. Date of blood draw for complete blood count:	13. Platelet count:
day mon year Date must be within the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).	If platelets $<$ 130,000 cells/mm ³ (mm ³ = μ L) at screening, patient is ineligible.
9. Hemoglobin:	
If hemoglobin < 10 g/dL at screening, patient is ineligible.	
10. Hematocrit:	
11. Mean corpuscular volume (MCV):	

C. Chemistries

Required at visits s, f24, f52, and f76.

14. Is metabolic panel required at this visit:

Y	es	N	lo .
(1)	(2)
		24.	J

15. Date of blood draw for chemistries:

	_		_
	day	mon	year
_			_

Date must be within the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).

16. Sodium:

mFa/I	

17. Potassium:

	•	
mE	a/I	

18. Chloride:

_		
	mEq/L	

19. Bicarbonate:

•	
mEq/L	

20. Calcium:

•	
mg/dL	

21. Blood urea nitrogen (BUN):

mg/dL	

22. Creatinine:

•	
 mg/dL	_

23. Uric acid:

•	
 mg/dL	_

D. Prothrombin time and INR

Required at all visits.

24. Date of blood draw for prothrombin time and INR:

	_		

mon

Date must be in the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).

25. Prothrombin time (PT):

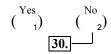


26. International normalized ratio (INR) (if INR > 1.4, patient is ineligible):

E. Hemoglobin A1c

Required at visits s, f24, f52, and f76.

27. Is HbA1c required at this visit:



28. Date of blood draw for HbA1c:

		_=
day	mon	vear

Date must be within the required time window; within 90 days of randomization or in the time window for the follow-up visit (check the patient's CyNCh visit time window guide).

29. HbA1c (if HbA1c is > 9.0% within 90 days of randomization, patient is ineligible):

	•	
 	<u> </u>	

F. Liver panel

Required at all visits.

30. Date of blood draw for liver panel:

day	mon	year

Date must be within the required time window; within 90 days of liver biopsy or in the time window for the follow-up visit (check the patient's CyNCh visit time window guide).

31. Bilirubin (total) [if total bilirubin > 3.0 mg/dL at screening, patient is ineligible]:

•	
 mg/dL	

32. Bilirubin (conjugated or direct) [if direct bilirubin > 1.0 mg/dL at screening, patient is ineligible]:

•	
mg/dL	

33. Aspartate aminotransferase (AST)

	U/L	

a. Upper limit of normal:

U/L	

34. Alanine aminotransferase (ALT)

U/L	

a. Upper limit of normal:



35. Alkaline phosphatase

U/L	

- **36.** Albumin (if albumin < 3.2 g/dL at screening, patient is ineligible):

•	
g/dL	

37. Total protein:

	•	
-	g/dL	

38. Gamma glutamyl transferase (GGT):

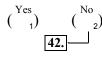
 U/L	·

G. Fasting lipid profile

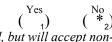
Required at visits s, f24, f52, and f76.

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw.

39. Is the lipid profile required at this visit:



40. Was participant fasting for at least 8 hours prior to blood draw:



*12 hour fasting is preferred, but will accept nonfasting lipid values.

41. Date of blood draw for fasting lipid profile:

day	mon	year

Date must be within the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).

- a. Triglycerides: ____ _ __ _ _ _
- **b.** Total cholesterol: $\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}\underline{\qquad}$
- c. HDL cholesterol level: ____ mg/dL ____
- **d.** LDL cholesterol level*: ____ mg/dL ____

*Enter "GT" if LDL cannot be calculated due to high triglycerides.

H. Fasting glucose and insulin

Required at visits s, f24, f52, and f76.

42. Are glucose and insulin required at this visit:

(Y	res 1)	(No	2
		45.	

43. Was participant fasting for at least 8 hours prior to blood draw:



*Patient must be fasting; 12 hour fasting is preferred. Fasting glucose and insulin must be obtained at visit s.

44. Date of blood draw for fasting glucose and insulin:

_		_
day	mon	year
Date must be within 9	0 days of live	r biopsy or i

Date must be within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).

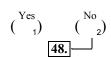
a. Serum glucose:

mg/dL	

I. Pregnancy test

Required at all study visits, if applicable.

45. Is pregnancy test applicable:



46. Date of urine collection (or blood draw):

		_=
dav	mon	vear

Date must be the same day as date of visit.

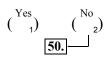
47. Pregnancy test result (if pregnancy test is positive at screening visit, patient is ineligible):

Positive (1

Negative (

J. Eligibility check

48. Is this the screening visit:



49. Was the patient found to be ineligible based on hemoglobin (item 9), WBC (item 12a), neutrophils (item 12b), platelet count (item 13), albumin (item 36), INR (item 26), HbA1c (item 29), bilirubin total (item 31), direct bilirubin (item 32), pregnancy test (item 47), or based on missing tests:



K. Administrative information

50. Study Physician PIN:

51. Study Physician signature:

52. Clinical Coordinator PIN: ____ ___

53. Clinical Coordinator signature:

day

54. Date form reviewed:

mon

year

LS - Laboratory Results Tests Done Only During Screening

Purpose: To record archival and current results of laboratory tests done only at screening.

When: Visit s.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. If is checked for any item the patient is not eligible for the CyNCh trial. If is checked for an item and the Study Physician agrees with the diagnosis, the patient is ineligible for CyNCh.

A. Center, patient, and visi	t identification	B. Screening etiologic tes	ts
1. Center ID:		8. Date of blood draw for to exclude viral cause	
2. Patient ID:		disease:	_
3. Patient code:		day Repeat if date is gr screening.	mon year reater than 2 years prior to
4. Date of visit:		a. Hepatitis B surface	e antigen (HBsAg):
	mon year	Positive	
5. Visit code:	_S	Negative	(2
6. Form & revision:	_1s2_	b. Hepatitis C antibo sult as negative if negative): Positive	dy (anti-HCV) (indicate re EIA is positive but RIBA i
7. Study:	CyNCh_8_		(Eug)—
		Negative	(2
		c. Hepatitis C virus R	RNA (HCV RNA):
		Positive	
		Negative	(2
		Not available	(3

C. Autoantibody studies

9. Date of blood draw for autoantibody tests:

day	mon	year
Repeat if date is	s greater than .	2 years prior to
screening.		

10. Anti-nuclear antibody (ANA):

Positive	(* 1)
Negative	(₂)
	12.

* If positive ANA value, complete either a or b depending on laboratory results.

a. Titer (record only the denominator):

	1/
Units:	•
	mg/dL

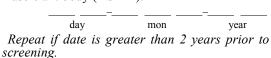
11. Is ANA titer greater than 1:80

b.



* Check Liver Biopsy Histology Findings Form for autoimmune liver disease.

12. Date of blood draw for anti-smooth muscle antibody (ASMA):



13. Anti-smooth muscle antibody (ASMA):

Positive	(* 1)
Negative	(2)
	14.

* If positive ASMA value, complete either a or b depending on laboratory results.

a. Titer (record only the denominator):

b. Units:



14. Date of blood draw for anti-mitochondrial antibody (AMA):

	<u> </u>	<u> </u>
day	mon	year
Repeat if date is	greater than 2	years prior to
screening.		

15. Anti-mitochondrial antibody (AMA):

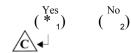
Positive	(* 1)
Negative	(2)
Not available	17. (₃)
	17.

* If positive AMA value, complete either a or b depending on laboratory results.

a. Titer (record only the denominator):

	1/
b. Units:	•
Di Cinto.	mg/dL

16. Is AMA titer greater than 1:80



* Check Liver Biopsy Histology Findings Form for primary biliary cirrhosis.

D. Ceruloplasmin

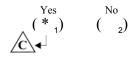
17. Date of blood draw for ceruloplasmin:

day	mon	year
Repeat if date screening.	is greater than	2 years prior to

18. Ceruloplasmin ____

Cciuiopiasiiiii	
_	mg/dL
a. Lower limit of normal:	•
	mg/dI

b. Is ceruloplasmin below the lower limit of normal:



* Check Liver Biopsy Histology Findings Form for Wilson's Disease.

E. Alpha-1 antitrypsin

19. Date of blood draw for alpha-1 antitrypsin (A1AT):

day	mon	year

Repeat if date is greater than 2 years prior to screening.

20. Alpha-1 antitrypsin (A1AT):

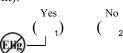
	31 \	mg/dL	
a. Lower	limit of normal:	ma/dI	

- 21. A1AT phenotype/genotype
 - **a.** SZ phenotype/genotype:

Yes	(1)
No	(2)
Unknown	(3)

ZZ pnenotype/genotype.		
Yes	(1
No	(2
Unknown	(3

22. Is A1AT deficiency a contributor to liver disease (physician judgment):

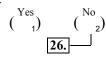


F. Iron

23. Date of blood draw for iron overload screening:

	 dav	mon		vear
Repeat if a screening.	date is gred		2 years	,
a. Serum iro	on:	-	μ <u>g</u>	/dL
b. Total Iro	n Binding C	Capacity: _		/dL

24. Is hepatic iron index available:



ng/mL

25. Hepatic iron index:

c. Ferritin:



G. Administrative information

26.	Study Physic	an PIN:		
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- 27. Study Physician signature:
- 28. Clinic Coordinator PIN:
- 29. Clinic Coordinator signature:
- **30.** Date form reviewed: day mon year

LT - Liver Tissue Banking

Purpose: To document collection of extra liver tissue and procedures for liver tissue banking.

When: Visits s and f52 when more than 2 cm of liver tissue are obtained during a biopsy. This form is expected when the Liver Biopsy Materials Documentation (SD) form says liver tissue was obtained for banking.

By whom: Clinical Coordinator, in consultation with study physician.

Instructions: Liver biopsy tissue should be obtained by a needle core biopsy (as opposed to a wedge biopsy) using a 16 gauge or greater needle. Whenever more than 2 cm of tissue are obtained during biopsy, place a 1-2 mm segment of liver tissue into a labeled 2.0 mL polypropylene cryovial pre-filled with approximately 1 mL of RNA*later*® Solution. Liver tissue should be placed in RNA*later*® Solution within one minute and no more than 5 minutes after biopsy. Note: If the sample is not placed in RNA*later*® Solution within 5 minutes, discard the cryovial. Refrigerate the cryovial at 4° C overnight to allow thorough penetration of the liver tissue and then transfer to -70° C freezer for storage. Batch ship cryovials monthly on dry ice to the NIDDK Biosample Repository located at Fisher BioServices.

A. Center, patient and visit identification	11. Was liver tissue refrigerated at 4° C overnight, then transferred to freezer for
1. Center ID:	storage:
2. Patient ID:	$ (Yes \atop 1) \qquad (No \atop 2) $ 12.
3. Patient code:	a. If no, describe conditions of local storage:
4. Date form initiated:	
day mon year	
5. Visit code (s or f52):	C. Cryovial label
6. Form & revision:1	12. Attach duplicate cryovial label (make sure you attach the duplicate of the label attached to the cryovial holding the liver tissue from this biopsy):
7. Study: CyNCh <u>8</u>	
B. Liver biopsy/RNA<i>later</i>® Solution storage procedures8. Date of biopsy:	
day mon year	
9. Was the liver tissue obtained from a needle core biopsy (as opposed to a wedge biopsy):	
$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$	D. Administrative information
10. Was liver tissue placed in RNA <i>later</i> ®	13. Clinical Coordinator PIN:
Solution preferably within 1 minute, but no more than 5 minutes after biopsy:	14. Clinical Coordinator signature:
$\binom{\operatorname{Yes}}{1} \qquad \binom{\operatorname{No}}{2}$	
* Discard liver tissue	15. Date form reviewed:
	day mon year

MR - MRI Consent and Report Form

Purpose: To document the collection and transmittal of MRI data.

When: Visit s and f52.

By whom: Study Radiologist/Study Physician and Clinical Coordinator.

Instructions: Complete this form based on the consent documents signed by the patient. Patient may still participate in CyNCh trial without an MRI. Please consult CyNCh SOP VI for additional procedures.

Before MRI examination review the following basic information with patient: 1) Patient should fast for four or more hours if possible before the MRI examination. 2) Necessary medications are allowed with small amounts of water. 3) Rehearse breathing instructions with patient. Patient will be asked to hold breath in end-inspiration to maximize breath-hold capacity and to reduce discomfort associated with breath-holding. 4) Explain the necessity of remaining still during the MRI examination.

On day of MRI examination confirm the following information with patient: 1) Patients identity. 2) MRI consent is signed and a copy of consent kept on site. 3) No MRI contraindications. 4) Émptied bladder prior to scanning. 5) Patient has been weighed, and been asked height. 6) MRI-compatible clothing (no metal or metallic/shiny clothing). 7) Breathing instructions rehearsed and understood (patient will be asked to hold breath in end-inspiration to maximize breath-hold capacity and reduce discomfort associated with breath-holding).

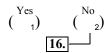
Pre-MRI preparation: 1) Patient to be positioned supine. 2) Ensure patient comfortable on scanner table. 3) For 3T MRIs, place dielectric pad over liver. 4) Place phased-array coil (over dielectric pad, for 3T scanners) centered over the liver; ensure good connection to scanner.

	Α.	Center,	patient	and	visit	id	entific	ation
--	----	---------	---------	-----	-------	----	---------	-------

- 1. Center ID:
- 2. Patient ID:
- 3. Patient code:
- **4.** Date form completed:

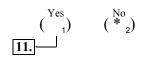
day	mon	year

- 5. Visit code:
- <u>m_r_1</u> **6.** Form & revision:
- CyNCh 8 7. Study:
- **8.** Is CyNCh MRI protocol currently in use at your center:



B. MRI results and information

9. Was an MRI performed:



^{*} Complete item 10, then skip to item 16.

- 10. Reason MRI not performed (check all that apply)
 - a. Patient did not consent to a MRI:
 - **b.** Patient was not fasting:
 - c. Patient suffers from extreme claustrophobia:
 - d. Patients weight or girth exceeds MRI scanner capabilities:
 - **e.** Other (specify):

	16.
Cechnician name:	

11. T

print name

12. Date and time of MRI:

	=	:	_
	day	mon	year
a. Time:			
	:	(,)) (,
hour	minute	am	/ (2 nm

Patient ID:		

- 13. Dates images sent to MRI Reading Center a. By CD/DVD: mon day year **b.** By secure in-server connection (enter "m" if not available): year D. Administrative information 14. Study Radiologist or Study Physician PIN: 15. Study Radiologist or Study Physician
- signature:
- **16.** Clinical Coordinator PIN:
- 17. Clinical Coordinator signature:
- **18.** Date form reviewed: day

mon

year

MV - Missed or Incomplete Visit

Purpose: Record the reason(s) for a missed or incomplete visit.

When: At the close of a visit window for any missed follow-up visit or for any follow-up visit with specific forms not completed. Use visit code f04, f12, f24, f36, f52 or f76.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in missing forms) within the time window for the visit.

A. Center, patient, and visit identification			10. Steps taken to avoid missing the visit (check all that apply)		
1. Center ID:			a. Telephoned patient:	(1)
			b. Mailed reminder card:	(1)
2. Patient ID:			c. Other (specify):	(1)
3. Patient code:			specify		
4. Date form completed:			14.	<u> </u>	J
day mon	year		D. Missed form information		
5. Visit code: <u>f</u>			11. Check form(s) not completed (check all that apply)		
6. Form & revision:m	<u>V</u>	1_	a. Blood Processing for Plasma and Serum (BP):	(1)
7. Study: CyNCh_8_		8	b. Follow-up Medical History (FH):	(1)
			c. Symptoms of Liver Disease (LP):	(1)
B. Reason for completion of this form			d. Laboratory Results - Tests Done During Screening and Follow-up (LR):	(1)
8. Was the entire visit missed:]	No	e. Liver Tissue Banking (LT):	(1)
(₁)	₂)	f. Nutrition Data Documentation for NDSR (ND):	(1)	
C. Missed visit information			g. Physical Examination (PE):	(1)
C. Misseu visit information			h. Focused Physical Examination (PF):	(1)
9. Reason for missed visit (check all that a	pply)		i. Parent Report for Teens (13-17) (PQ):	(1)
a. Patient was ill:b. Patient was temporarily away from	(1)	j. Pediatric QOL: Parent Report for Child (8-12) (PR):	(1)
area:	(1)	k. Pediatric QOL: Child Report (PW):	(1)
c. Patient refused to return:	(1)	l. Pediatric QOL: Teen Report (PY):	(1)
d. Patient has permanently moved from the area:	(1)	m. Study Drug Dispensing and Return (RD):	(1)
e. Unable to contact patient:	(1)	n. Liver Biopsy Materials Documentation (SD):	(1)
f. Other (specify):	(1)	o. MRI Consent and Report Form (MR):	(1)
specify			p. Other (specify):	(1)
			specify		

12.	Reason form(s) not completed (check all that apply)		
	a. Patient was ill:	(1
	b. Patient/parent refused procedure:	(1.
	c. Procedure forgotten:	(1.
	d. Other (specify):	(1.
	specify		
13.	Attempts made to complete form(s) (check all that apply)		
	a. Attempted to reschedule procedure:	(1.
	b. Attempted to collect interview data by phone from patient/parent:	(1.
	c. Attempted to gain patient/parent cooperation:	(1.
	d. Other (specify):	(1.
	specify		
E. A	Administrative information		
14.	Clinical Coordinator PIN:		
15.	Clinical Coordinator signature:		
16.	Date form reviewed:		
	day mon	year	

ND - Nutrition Data Documentation

Purpose: To document completion of the 24-hour food recall using NDS-R on three different days. **When**: Visit s and f52.

Administered by: Clinical Coordinator.

Instructions: Complete this form after the patient has completed the 24-hour food recalls using the NDS-R. Attach a copy of the NDS-R Record Properties Report for each recall to this form.

A. Center, patient, and visit identification			10. Who was the respondent (check all that apply)				
1. Center ID:			a. Patient:	(1.		
<u> </u>			b. Patient's mother or female guardian:	(1.		
2. Patient ID:			c. Patient's father or male guardian:	(1/		
3. Patient code:			d. Other (specify):	(1.		
4. Date form initiated (cannot precede the dat of the first diet recall):	e		specify				
			11. NDS-R record properties report				
day mon y	ear		a. Energy:kilocaloric				
5. Visit code:			Kilocalolik	,3			
		<u></u>	b. Total fat:				
6. Form & revision: _n_d_		2	grams				
7. Study: CyNC	h .	8	c. Total saturated fatty acids (SFA):	•			
B. Administration of food recall #1			grams				
8. Date of 24-hour food recall #1:			d. Total carbohydrates:				
	ear		grams				
9. How was the NDS-R food recall completed (you must check at least three)			e. Total sugars: grams	<u> </u>			
a. Interview in English:	(1)	f. Total protein:)			
b. Interview with translator: (check a or b or both)	(1)	grams				
c. Interview in person:	(1)					
d. Interview by phone: (check either c or d)	(1)					
e. Administered by dietician:	(1)					
f. Administered by Clinical Coordinator:	(1)					
g. Administered by other (specify): (check either e, f, or g)	(1)					
specify							

C. Administration of food recall #2					D. Administration of food recall #3				
12. Date of 24-hou	r food re	ecall #2:			16. Date of 24-hour food recall #3:				
da		mon	year		day mon	year			
13. How was the N completed (you		ood recall heck at least three)		17. How was the NDS-R food recall completed (you must check at least three)				
a. Interview in	English	:	(1)	a. Interview in English:	(1)		
b. Interview w (check a or			(1)	b. Interview with translator: (check a or b or both)	(1)		
c. Interview in	person:		(1)	c. Interview in person:	(1)		
d. Interview by (check eithe			(1)	d. Interview by phone: (check either c or d)	(1)		
e. Administere	d by die	tician:	(1)	e. Administered by dietician:	(1)		
f. Administere	d by Cli	nical Coordinator:	: (1)	f. Administered by Clinical Coordinator:	(1)		
g. Administere (check eithe			(1)	g. Administered by other (specify): (check either e, f, or g)	(1)		
		specify			specify				
14. Who was the re	esponde	nt (check all that a	apply))	18. Who was the respondent (check all that ap	oply)			
a. Patient:			(1)	a. Patient:	(1)		
b. Patient's mo	other or	female guardian:	(1)	b. Patient's mother or female guardian:	(1)		
c. Patient's fat	her or m	ale guardian:	(1)	c. Patient's father or male guardian:	(1)		
d. Other (spec	ify):		(1)	d. Other (specify):	(1)		
		specify			specify				
15. NDS-R record	properti	es report			19. NDS-R record properties report				
a. Energy:					a. Energy:				
		kilocalori	ies		kilocalorie	S			
b. Total fat:		•	•		b. Total fat:				
		grams			grams				
c. Total satura	ted fatty	acids (SFA):			c. Total saturated fatty acids (SFA):				
	-	grams	<u> </u>		grams		—		
		8-3			g				
d. Total carbol	nydrates	:	•		d. Total carbohydrates:				
	_	grams			grams				
e. Total sugars	: _	grams	•		e. Total sugars:				
		grams			grans				
f Total proteir	١٠	•	•		f Total protein:				

grams

grams

Patient ID:	 	

D A	dministr	ative ir	ıfarm:	ation

20.	Version of NDS-R used: 2	0	1	
21.	Clinical Coordinator PIN:			
22.	Clinical Coordinator signature:			
23.	Date form reviewed:			

day mon year Attach copy of the NDS-R Record Properties Re-port for each 24-hour recall to this form.

PE - Physical Examination

Purpose: Record detailed physical exam findings.

When: Visits s, f24, f52, and f76.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurements are found in the CyNCh SOP, Part I. In brief: Height, weight, waist and hips all should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

One of the eligibility criteria for CyNCh is the ability to swallow CyNCh study medications. If you are unsure about the patient's ability to swallow the study medication, you may ask the patient to swallow a capsule from the bottle of capsules sent to the clinical center by the DCC before the start of CyNCh. The physical examination might be a logical time to ask the patient about this/ask for a demonstration. If the patient is unable to swallow the capsule and is ineligible (item 30=2), the PE form should not be keyed.

A. Center, patient, and visit identification			9. Weight (shoes off)	
1. Center ID:			a. Weight, 1st measurement:	•
2. Patient ID:			b. Weight, 2nd measurement:	
3. Patient code:			c. Units:	•
			Pounds	(,
4. Visit date:			Kilograms	
day 5. Visit code:	mon	year	10. Waist (standing, at midpoint be of iliac crest and lowest par repeat waist measurements measurements within 4 in (10.	rt of costal margin until you have two
6. Form & revision:		_pe1_	a. Circumference, 1st measure	ement:
7. Study:		CyNCh 8	b. Circumference, 2nd measur	st circumference rement:
B. Measurements			wai	st circumference
8. Height (shoes off)			c. Units: Inches	si circumicionec
a. 1st measurement:		•	Centimeters	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$
b. 2nd measurement:		<u> </u>		
c. Units:				
Inches		$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
Centimeters		(,)		

11. Hip (standing, at fullest part of		17. Acanthosis nigricans (check only	one):
measurements until you hav within 4 in (10.2 cm) of each	ve two measurements cother)	Absent (not detectable on close i	$nspection) \begin{pmatrix} 0 \end{pmatrix}$
a. Circumference, 1st measu	•	Present (clearly present on close inspection, not visible to casual cextent not measurable)	observer,
b. Circumference, 2nd measure.	ip circumference urement: ip circumference	Mild (limited to base of skull, no extending to lateral margins of n < 3 inches in breadth)	t
c. Units: Inches Centimeters 12. Temperature (Oral)	(₁) (₂)	Moderate (extending to lateral m of neck, 3-6 inches in breadth, no from patient's front) Severe (extending anteriorly, > 6 breadth, visible from front)	argins ot visible (3)
a. Degrees:		18. Other skin abnormality <i>(check ala</i>	
b. Scale: Fahrenheit Centigrade	$\begin{pmatrix} & & 1 \\ & & 2 \end{pmatrix}$	a. Jaundice:b. Palmar erythema:c. Spider angiomata:	
13. Blood pressure	X 2	d. Striae:e. Skin lesions:	(₁)
a. Systolic:b. Diastolic:	mmHg mmHg	f. Other (specify): g. None of the above:	(1)
14. Resting radial pulse:	beats/minute	19. Head, eyes, ears, nose, throat: Normal	(.)
15. Respiratory rate:	breaths/minute	Abnormal	20. (₂)
C. Examination findings		specify abnormality	y
16. Skin: Normal Abnormal	(₁)	20. Neck: Normal	(₁)
Achormai	(2)	Abnormal specify abnormality	()
		21. Lymphatic:	
		Normal	(1)
		Abnormal	(2)

specify abnormality

22.	Chest and lungs:	
	Normal	(1)
	Abnormal	(₁) (₂)
	specify	
23.	Heart:	
	Normal	(1)
	Abnormal	24. (₂)
	specify abnormality	
24.	Abdomen:	
	Normal	(₁)
	Abnormal	26. (₂)
25.	Abdomen abnormality (check all that apply)	
	a. Ascites:	(₁)
	b. Obese:	(1)
	c. Hepatomegaly: (if checked, span from right midcla line):	evicular (1)
		cm
	d. Splenomegaly:	(1)
	e. Other (specify):	(1)
26.	Extremities:	
	Normal	(1)
	Abnormal	(₁) (₂)
27.	Abnormality of the extremities (check all that apply)	
	a. Contractures:	(1)
	b. Joint hyperextension:	(1)
	c. Muscle wasting:	(1)
	d Palmar erythema:	()

28.	Nervous	system:
-0.	ricivous	System.

Not performed	(0
Normal	(1)
Abnormal	(2)
specify		

D. Ability to swallow study medication

(At the randomization visit the Study Physician/Clinical Coordinator will be asked to provide assurance that the patient is able to swallow the CyNCh study medication; if needed, you could ask the patient to swallow a placebo capsule).

29. Is this the screening visit:

Yes (Yes	$\binom{\text{No}}{2}$
	31.

30. Was the patient able to swallow a placebo capsule *(check only one)*:

Yes, patient was able to swallow capsule	(1)
No, patient was unable to swallow the	,	,
capsule) K	2)

Did not ask for a demonstration at this time (3.

E. Administrative information

- **31.** Study Physician PIN:
- **32.** Study Physician signature:
- 33. Clinical Coordinator PIN:
- **34.** Clinical Coordinator signature:

35. Date form reviewed:		
_		_
day	mon	year

e. Pedal edema:f. Other (specify):

specify

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.

When: Visits f04, f12, f36.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

Instructions: Details of the protocol for height, weight, waist and hip measurement are found in the CyNCh SOP Part I. In brief: height, weight, waist and hips should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

A. Center, patient, and visi	it identi	fication	10. Waist (standing, at midpoint be	
1. Center ID:			of iliac crest and lowest par repeat waist measurements measurements within 4 in (10.	until you have two
2. Patient ID:			a. 1st measurement:	•
3. Patient code:			b. 2nd measurement:	
4. Visit date:			c. Units:	- — • —
_		_	Inches	()
day	mon	year	Centimeters	$\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$
5. Visit code:			11. Hip (standing, at fullest part of measurements until you have within 4 in (10.2 cm) of each of	two measurements
6. Form & revision:		<u>p</u>	, , ,	nner)
7. Study:		CyNCh 8	a. 1st measurement:	•
B. Measurements			b. 2nd measurement:	•
8. Height (shoes off)			c. Units:	
a. 1st measurement:			Inches	(1)
		•	Centimeters	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
b. 2nd measurement:		•	12. Temperature (oral)	
c. Units:			a. Degrees:	•
Inches		(1)		
Centimeters		$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$	b. Scale:	()
A W. 1 . / 1			Fahrenheit:	(1)
9. Weight (shoes off)			Centigrade:	(₂)
a. 1st measurement:		•	13. Blood pressure	
b. 2nd measurement:			a. Systolie:	
c. Units:			b. Diastolic:	
Pounds		(.)	b. Diustone.	mmHg
Kilograms		()		

Resting radial pulse:	beats/minute	D. Administrative information
Respiratory rate:	breaths/minute	18. Study Physician ID:
Liver signs		19. Study Physician signature:
Liver and spleen:		
Normal	(1)	20. Clinical Coordinator ID:
Abnormal	18. (₂)	21. Clinical Coordinator signature:
Abnormality (check all that a	pply)	
a. Ascites:	(1)	
b. Asterixis:	(1)	22. Date form reviewed:
c. Contractures:	(1)	
d. Fetor:	(1)	day mon yea
e. Hepatomegaly:	(1)	
If Yes, span from right mid	lclavicular line:	
f. Jaundice:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$	
f. Jaundice:g. Muscle wasting:	(₁) (₁)	
g. Muscle wasting:	(1)	
g. Muscle wasting:h. Palmar erythema:	(₁)	
g. Muscle wasting:h. Palmar erythema:i. Pedal edema:	(₁) (₁) (₁)	

PQ – Pediatric Quality of Life: Parent Report for Teens (Age 13-17)

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of teens, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #8, Instructions for Pediatric Quality of Life (Forms PQ and PR) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQL™ creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	nter, patient, and visit iden	tification		Iministrative information To be completed by Clinical Coordinator	after	
1.	Center ID:		Si	urvey is completed.)		
2.	Patient ID:		8.	How was the Pediatric Quality of Life questionnaire completed:		
3.	Patient code:			Salf administrated in English	(,
4.	Date form completed:			Self-administered in English Self-administered in Spanish Interview in English Interview in Spanish	(2)
	day mon	year		merview in Spanish	(4)
5.	Visit code:		9.	Clinical Coordinator a. PIN: b. Signature:		
6.	Form & revision:	<u>p q 1</u>				
7.	Study:	CyNCh <u>8</u>	10.	Date form reviewed:		
				day mon	year	

Affix label here
Patient ID:
Patient code:
Visit code:

PQ - Pediatric Quality of Life: Parent Report for Teens (Age 13-17)

In the past **ONE month**, how much of a **problem** has your teen had with...

PHYSICAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:	0	1	2	3	4
13. Participating in sports activity or exercise:	0	1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores around the house:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:	0	1	2	3	4

EMOTIONAL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	Feeling angry:	0	1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

soc	SOCIAL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
24.	Getting along with other teens:	0	1	2	3	4
25.	Other teens not wanting to be his or her friend:	0	1	2	3	4
26.	. Getting teased by other teens:		1	2	3	4
27.	7. Not able to do things that other teens his or her age can do:		1	2	3	4
28.	Keeping up with other teens:	0	1	2	3	4

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Affix label here						
Patient ID:						
Patient code:						
Visit code:						

SCHOOL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	31. Keeping up with schoolwork:		1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PR – Pediatric Quality of Life: Parent Report for Children (Age 8-12)

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Parent of child, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #8, Instructions for Pediatric Quality of Life (Forms PQ and PR) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQL™ creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Center, patient, and visit identification				B. Administrative information (To be completed by Clinical Coordinator after						
1.	Center ID:		_ survey is completed.)							
2.	Patient ID:		8.	How was the Pediatric Quality of Life questionnaire completed:	;					
3.	Patient code:			Calcadaria danadia Fastida	(,				
4.	Date form completed:			Self-administered in English Self-administered in Spanish Interview in English Interview in Spanish	(2)				
	day mon	year		interview in Spanish	(4)				
5.	Visit code:		9.	Clinical Coordinator a. PIN: b. Signature:						
6.	Form & revision:p_	<u>r</u> <u>1</u>		<u> </u>						
7.	Study:	CyNCh 8	10.	Date form reviewed:						
				day mon	year					

Affix label here							
Patient ID:							
Patient code:							
Visit code:							

PR - Pediatric Quality of Life: Parent Report for Children (Age 8-12)

In the past **ONE month**, how much of a **problem** has your child had with...

PHYSICAL FUNCTIONING (problems with)		Almost Never	Some- times	Often	Almost Always
11. Walking more than one block:	0	1	2	3	4
12. Running:		1	2	3	4
13. Participating in sports activity or exercise:		1	2	3	4
14. Lifting something heavy:	0	1	2	3	4
15. Taking a bath or shower by him or herself:	0	1	2	3	4
16. Doing chores around the house:	0	1	2	3	4
17. Having hurts or aches:	0	1	2	3	4
18. Low energy level:		1	2	3	4

EMOTIONAL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
19.	Feeling afraid or scared:	0	1	2	3	4
20.	Feeling sad or blue:	0	1	2	3	4
21.	21. Feeling angry:		1	2	3	4
22.	Trouble sleeping:	0	1	2	3	4
23.	Worrying about what will happen to him or her:	0	1	2	3	4

Soc	IAL FUNCTIONING (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	Getting along with other children:	0	1	2	3	4
25.	Other kids not wanting to be his or her friend:	0	1	2	3	4
26.	. Getting teased by other children:		1	2	3	4
27.	Not able to do things that other children his or her age can do:	0	1	2	3	4
28.	Keeping up when playing with other children:	0	1	2	3	4

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Affix label here
Patient ID:
Patient code:
Visit code:
L

SCHOOL FUNCTIONING (problems with)		Never	Almost Never	Some- times	Often	Almost Always
29.	Paying attention in class:	0	1	2	3	4
30.	Forgetting things:	0	1	2	3	4
31.	31. Keeping up with schoolwork:		1	2	3	4
32.	Missing school because of not feeling well:	0	1	2	3	4
33.	Missing school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PW – Pediatric Quality of Life: Child Report (Age 8-12)

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #7, Instructions for Pediatric Quality of Life (Forms PW and PY) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Center, patient, and visit identification				B. Administrative information (To be completed by Clinical Coordinator after					
1.	Center ID:			Si	ırvey is completed	1.)			
2.	Patient ID:			8.	How was the Pe	diatric Quality of Li ompleted:	ife		
3.	Patient code:				0.10.1	1' F 1' 1		,	
4.	Date form completed:		_		Self-administere Self-administere Interview in Eng Interview in Spa	ed in Spanish glish	(1) 2) 3) 4)	
	day m	on	year		interview in Spe	111311	(4)	
5.	Visit code:			9.	Clinical Coordina. PIN: b. Signature:				
6.	Form & revision:	<u> </u>	<u>w</u> 1		8				
7.	Study:		CyNCh 8	10.	Date form revie	wed:			
					a	mon	- year		

Affix label here						
Patient ID:						
Patient code:						
Visit code:						

PW - Pediatric Quality of Life: Child Report (Age 8-12)

In the past **ONE month**, how much of a **problem** has this been for you...

ABOUT MY HEALTH AND ACTIVITIES (problems with)		Almost Never	Some- times	Often	Almost Always
11. It is hard for me to walk more than one block:	0	1	2	3	4
12. It is hard for me to run:	0	1	2	3	4
13. It is hard for me to do sports activity or exercise:	0	1	2	3	4
14. It is hard for me to lift something heavy:	0	1	2	3	4
15. It is hard for me to take a bath or shower by myself:	0	1	2	3	4
16. It is hard for me to do chores around the house:	0	1	2	3	4
17. I hurt or ache:	0	1	2	3	4
18. I have low energy:	0	1	2	3	4

ABOUT MY FEELINGS (problems with)		Never	Almost Never	Some- times	Often	Almost Always
19.	I feel afraid or scared:	0	1	2	3	4
20.	I feel sad or blue:	0	1	2	3	4
21.	I feel angry:	0	1	2	3	4
22.	I have trouble sleeping:	0	1	2	3	4
23.	I worry about what will happen to me:	0	1	2	3	4

HOW I GET ALONG WITH OTHERS (problems with)		Never	Almost Never	Some- times	Often	Almost Always
24.	I have trouble getting along with other kids:	0	1	2	3	4
25.	Other kids do not want to be my friend:	0	1	2	3	4
26.	Other kids tease me:	0	1	2	3	4
27.	I cannot do things that other kids my age can do:	0	1	2	3	4
28.	It is hard to keep up when I play with other kids:	0	1	2	3	4

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Affix label here					
Patient ID:					
Patient code:	İ				
Visit code:					

ABOUT SCHOOL (problems with)		Never	Almost Never	Some- times	Often	Almost Always
29.	It is hard to pay attention in class:	0	1	2	3	4
30.	I forget things:	0	1	2	3	4
31.	I have trouble keeping up with my schoolwork:	0	1	2	3	4
32.	I miss school because of not feeling well:	0	1	2	3	4
33.	I miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

PY – Pediatric Quality of Life: Teen Report (Age 13-17)

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

Administered by: Self-administered. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #7, Instructions for Pediatric Quality of Life (Forms PY and PW) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Center, patient, and visit identification			B. Administrative information (To be completed by Clinical Coordinator after							
1.	Center ID:		survey is completed.)							
2.	Patient ID:		8.	How was the Pe	ediatric Quality of Li ompleted:	ife				
3.	Patient code:			0.10.1	1: E 1:1	,	,			
4.	Date form completed:			Self-administered Self-administered Interview in Englinterview in Spa	ed in Spanish glish	(1) 2) 3)			
	day mon	year		merview in Spa	1111511	(4)			
5.	Visit code:		9.	Clinical Coordina. PIN: b. Signature:						
6.	Form & revision:	<u>p</u> <u>y</u> 1		C						
7.	Study:	CyNCh 8	10.	Date form revie	wed:					
					mon	year				

PY	' - Pediatric Quality of Life	:
	Adolescent (Age 13-17)	

Affix l	abel here
Patient ID:	
Patient code:	
Visit code:	———

In the past **ONE month**, how much of a **problem** has this been for you...

ABO	UT MY HEALTH AND ACTIVITIES (problems with)	Never	Almost Never	Some- times	Often	Almost Always
11.	It is hard for me to walk more than one block:	0	1	2	3	4
12.	It is hard for me to run:	0	1	2	3	4
13.	It is hard for me to do sports activity or exercise:	0	1	2	3	4
14.	It is hard for me to lift something heavy:	0	1	2	3	4
15.	It is hard for me to take a bath or shower by myself:	0	1	2	3	4
16.	It is hard for me to do chores around the house:	0	1	2	3	4
17.	I hurt or ache:	0	1	2	3	4
18.	I have low energy:	0	1	2	3	4

ABOUT MY FEELINGS (problems with)		Almost Never	Some- times	Often	Almost Always
19. I feel afraid or scared:	0	1	2	3	4
20. I feel sad or blue:	0	1	2	3	4
21. I feel angry:	0	1	2	3	4
22. I have trouble sleeping:	0	1	2	3	4
23. I worry about what will happen to me:	0	1	2	3	4

How	I GET ALONG WITH OTHERS (problems with)	Never	Almost Never	Some- times	Often	Almost Always
24.	I have trouble getting along with other teens:	0	1	2	3	4
25.	Other teens do not want to be my friend:	0	1	2	3	4
26.	Other teens tease me:	0	1	2	3	4
27.	I cannot do things that other teens my age can do:	0	1	2	3	4
28.	It is hard to keep up with my peers:	0	1	2	3	4

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Affix label here
Patient ID:
Patient code:
Visit code:
L

ABOUT SCHOOL (problems with)	Never	Almost Never	Some- times	Often	Almost Always
29. It is hard to pay attention in class:	0	1	2	3	4
30. I forget things:	0	1	2	3	4
31. I have trouble keeping up with my schoolwork:	0	1	2	3	4
32. I miss school because of not feeling well:	0	1	2	3	4
33. I miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

CyNCh

RC - Rescreen in CyNCh

Purpose: To rescreen a patient who was previously found to be ineligible for the CyNCh Trial due to a temporary ineligibility. This form must be the first form completed and keyed for the patient for this screening cycle (the date in item 4 of this form will be the date that the 120-day screening window starts). The original RG form completed for the patient must remain in the data system. New screening labels will be available for printing upon keying this form.

When: Visit code s.

Administered by: Clinical Coordinator.

Respondent: None.

Instructions: Complete this form for a patient who was previously found to be ineligible for CyNCh due to a temporary ineligibility and who now wants to rescreen for CyNCh. In general, the patient must complete all CyNCh screening data collection anew and all previously keyed CyNCh screening forms should be deleted from the data system except the RG and possibly the CG form. If needed, update section C (only education and employment history) of the RG form and update the keyed record (you cannot delete the RG form); note that the patient's age will not change since it is based on the date of the RG form. If any changes are made in section C, the review date in section F should be updated. If blood was collected successfully for the Genetics Repository, a new sample does not need to be collected and the previously completed CG form may remain unchanged in the data system. Plasma and serum must be collected anew.

A. Center, patient, and visit identification		C. Administrative information					
1. Center ID:		9. Clinical Coordinator PIN:					
2. Patient ID:		10. Clinical Coordinator signature:					
3. Patient code:		_					
4. Date of visit:		11. Date form reviewed:					
day	mon year	day	mon	year			
5. Visit code:	<u> </u>						
6. Form & revision:	<u>r</u> <u>c</u> <u>1</u>						
7. Study:	CyNCh 8						
B. CyNCh participation							
8. Date in item 4 of origin form:	nal CyNCh RG						
	mon year						

Purpose: To explain CyNCh study drug prescription dose instructions and to record dispensing and return of study drug. **When:** Visits rz, f04, f12, f24, f36, and f52. Use visit code "n" if study drug is dispensed or returned at a time other than study visits or if a second form is needed at a visit to document returned study drug.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Instructions: CyNCh study drug will be taken orally in the morning and in the evening 30 minutes prior to meals. Children should be instructed to take 75 mg capsules according to their weight group:

≤65 kg at baseline	4 capsules twice daily	600 mg/day
>65-80 kg at baseline	5 capsules twice daily	750 mg/day
>80 kg at baseline	6 capsules twice daily	900 mg/day

This form documents dispensing of CyNCh study drug, return of unused study drug, return of empty study drug bottles, and is required at visit rz, f04, f12, f24, f36, and f52.

The children and their parents/ guardians should be queried about return of empty study drug bottles at all study visits. The clinical coordinator should count and record the number of capsules remaining in the study drug bottles each time a patient returns used study drug bottles to the clinical center. This form allows recording of the return of up to 12 bottles. If more than 12 bottles are returned, complete a second form (using visit code "n") to record the information for the remaining bottles.

Study drug taken orally will be increased gradually during weeks 1-4 to the prescribed dose for the weight group and will remain fixed at that dose thereafter, regardless of weight changes, according to the following dosing schemes:

≤65 kg at baseline	Week 1: Week 2: Week 3: Weeks 4-52:	1 capsule twice daily (150 mg/day) 2 capsules twice daily (300 mg/day) 3 capsules twice daily (450 mg/day) 4 capsules twice daily (600 mg/day)
>65-80 kg at baseline	Week 1: Week 2: Week 3: Weeks 4-52:	2 capsules twice daily (300 mg/day) 3 capsules twice daily (450 mg/day) 4 capsules twice daily (600 mg/day) 5 capsules twice daily (750 mg/day)
>80 kg at baseline	Week 1: Week 2: Week 3: Weeks 4-52:	3 capsules twice daily (450 mg/day) 4 capsules twice daily (600 mg/day) 5 capsules twice daily (750 mg/day) 6 capsules twice daily (900 mg/day)

Study drug will be dispensed in bottles including 150 capsules of 75 mg strength as specified below:

Weight group	Visit Number of Bottles/capsules		Comments	
≤65 kg at baseline	rz	2	300	4 week supply $+ 2.8$ weeks
	f04	4	600	8 week supply + 2.7 weeks
	f12	6	900	12 week supply + 4.1 weeks
	f24	6	900	12 week supply + 4.1 weeks
	f36	7	1,050	16 week supply $+$ 2.8 weeks
>65 kg - ≤80 kg at baseline	rz	3	450	4 week supply + 3.6 weeks
	f04	5	750	8 week supply + 2.7 weeks
	f12	7	1,050	12 week supply + 3 weeks
	f24	7	1,050	12 week supply + 3 weeks
	f36	9	1,350	16 week supply $+$ 3.3 weeks
>80 kg at baseline	rz	3	450	4 week supply + 2.4 weeks
G	f04	6	900	8 week supply + 2.7 weeks
	f12	8	1,200	12 week supply + 2.3 weeks
	f24	8	1,200	12 week supply + 2.3 weeks
	f36	11	1,650	16 week supply + 3.6 weeks

Α.	Center.	patient,	and	visit	identifi	ration
/l.	Center,	patient,	anu	VISIL	IUCIIUIII	cation

- 1. Center ID: _____ _____
- 2. Patient ID:
- **3.** Patient code: _____ ____
- 4. Date of visit:

_		_
day	mon	year

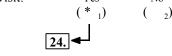
- **5.** Visit code: _____
- **6.** Form & revision: <u>r d 1</u>
- 7. Study: CyNCh <u>8</u>

B. Study drug dispensing

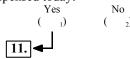
8. Is this a second form for returning additional drug bottles at this visit:

Yes

No



- * Key first form before this form.
- **9.** Will study drug be dispensed today:



- **10.** Reason for not dispensing study drug *(check all that apply)*
 - **a.** Not a scheduled study drug dispensing visit:
 - **b.** Study physician-directed treatment interruption/termination: (
 - **c.** Unwillingness of the patient to take study drug:
 - d. Other (specify):

specify	y	
		24

11. How many bottles were dispensed: (01-11)

Bottle tear-off label

- 12.

 Affix label here
- 13.

 Affix label here
- 14.

 Affix label here
- 15.

 Affix label here
- Affix label here
- 17.

 Affix label here
 - Affix label here

18.

 $\begin{pmatrix} 1 \end{pmatrix}$

Patient ID:	
i auciii iD.	

19.	
	Affix label here



21.	
	Affix label here

22.	[
	Affix label here

23. How was the study drug dispensed to the patient *(check only one)*:

In person Mail Other (specify)		(1) 2) 3)
	specify		

24.	Were any bottles returned at this v	isit:	
	Y	es	No
	(1)	(2
		39	9.]◀

25. Number of bottles returned (if more than 12 bottles are returned, complete a second RD form):

(01	-12)

a.	b.
Bottle No.	Number of
	capsules returned

26.	
	(000-150)

D. Remaining bottles

38. Are any additional bottles being returned:

Yes

No $\begin{pmatrix} & & & & & & \\ & & & & & \\ & & & & & \end{pmatrix}$

*If yes, complete a second RD form using visit code "n."

Patient ID:		

IMPORTANT: You must enter this form into the data system **within 48 hours** of dispensing study drug to the participant.

39. Study Physician PIN:

40. Study Physician signature:

41. Clinical Coordinator PIN:

42. Clinical Coordinator signature:

43. Date form reviewed:

E. Administrative information

day mon year

RG - Registration

Purpose: To register patient as candidate for enrollment in CyNCh and to assign a patient ID number. This is the first form completed for a CyNCh patient. The Registration Form must be the first form keyed, before any other CyNCh forms.

When: At first screening visit (s).

Administered by: Clinical Coordinator.

Respondent: Patient and guardian.

Instructions: Use Flash Cards as instructed. Do not assign a new ID if patient has previously been assigned an ID for a NASH CRN study. If is checked for any item, the patient is not eligible for CyNCh and the form should not be keyed.

A. Center, patient and visi	t identificati	on
1. Center ID:		
2. Patient ID:		
3. Patient code:		
4. Visit date:		
day	mon	year
5. Visit code:	S	
6. Form & revision:	<u>r</u>	<u>g</u> 1

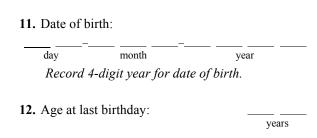
C. Information about patient

Not using assent

Yes No

10. Has the patient signed the CyNCh informed assent statement:

Not using assent for this age child



B. Consent

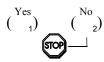
7. Study:

8. After reviewing the existing records (e.g., liver biopsy, elevated aminotransferases, and/or history) does the study physician feel that the patient may be suitable for the study:

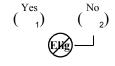


CyNCh 8

9. Has the patient (or patient's guardian) signed the CyNCh informed consent statement:



13. Is the patient's age at least 8 years old and less than 18 years:



14. Gender:

Male	(1
Female	(2

15. Ethnic category (show the patient/guardian Flash Card #1 and ask the respondent to pick the category that describes the patient best; check only one):

Hispanic or Latino or Latina	(1
Not Hispanic, not Latino, not Latina	(2
	17.]

16. What describes the patient's Hisp Latino, or Latina origin best (shiftent/guardian Flash Card #1 and dent to pick the subcategory that be patient's Hispanic, Latino, or Lationly one):	now the pa- d ask the respon- pest describes the	20. Combined annual income before taxes of all members of patient's household (show guardian Flash Card #4 and ask respondent to pick the category that describes the patient's combined household income best; check only one):
• •	()	Less than \$15,000 (₁)
Mexican	(1)	\$15,000 - \$29,999 (₂)
Puerto Rican	(₂)	\$30,000 - \$49,999 (3)
Cuban	(3)	\$50,000 or more $\binom{4}{4}$
South or Central American	(4)	D. D. J. J. J. J. WIGH ODN J. J.
Other Spanish culture or origin	$\begin{pmatrix} & & \\ & & 5 \end{pmatrix}$	D. Previous registration in a NASH CRN study
specify		21. Has the patient ever been assigned an ID number in a NASH CRN study:
17. Racial category (show the patient Card #2 and ask the respondent gory or categories that describe check all that apply)	to pick the cate-	$\binom{\text{Yes}}{1} \qquad \binom{\text{No}}{2}$ $\boxed{25.}$
a. American Indian or Alaska Na	tive: $\binom{1}{1}$	22. In which NASH CRN studies has the
b. Asian:	(1)	patient previously been registered (check all that apply)
c. Black, African American, Neg	•	a. NAFLD Database: (1)
Haitian:	(1)	b. TONIC: (₁)
d. Native Hawaiian or other Paci		c. NAFLD Pediatric Database 2:
Islander:	(1)	d. Other, (specify):
e. White:	(1)	(1)
f. Patient/guardian refused:	(1)	specify
18. In what country was the patient b <i>one</i>):	orn (check only	23. ID Number previously assigned to patient (record patient ID in item 2):
Continental US (includes Alaska) Hawaii	()	patient 1D in tiem 2).
Other, (specify):	(1)	24. Code previously assigned to patient <i>(record pa-</i>
Other, (spectyy):	(2)	tient code in item 3):
specify		
19. Patient's current grade level in sc home school) (show the patient, Card #3 and ask the respondent gory that describes the patient time, report grade entering in the one):	/guardian Flash to pick the cate- best; if summer	E. ID assignment (If a STOP or ineligible condition was checked in section B, the patient is ineligible and a Patient ID should not be assigned. If the patient was pre-
Grades 1 to 5	(1)	viously registered in a NASH CRN study, a new ID number should not be assigned.)
Grades 6-8	$\begin{pmatrix} & & & & & & \\ & & & & & & \end{pmatrix}$,
Grades 9-12	$\begin{pmatrix} & 2 \\ & 3 \end{pmatrix}$	25. Place ID label below and record Patient ID in item 2 and patient code in item 3.
Other, (specify):	(4)	11) in tem 2 and patient code in tem 3.
specify		CCCC ####,zzz

Patient ID:		

F. Administrative information

26. Clinical Coordinator PIN:

27. Clinical Coordinator signature:

28. Date form reviewed:

mon

year

CyNCh

RZ - Randomization Checks

Purpose: To check eligibility for CyNCh with respect to items not checked elsewhere on CyNCh screening forms and record reasons for ineligibility for patients found to be ineligible.

When: Visit rz.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: This form may be initiated at any time. If the patient proceeds to randomization, it must be reviewed on the day of randomization. Patients of childbearing potential must complete the randomization day pregnancy test at the clinic on the day of randomization. Height and weight must be obtained on the day of randomization.

If \mathfrak{S} is checked for any item, complete the entire form, but note that the patient may not participate in the CyNCh trial. If an item has not been assessed because the patient is ineligible, write " \mathbf{m} " (missing) next to that item. This form must be keyed for each patient for whom form RG was completed.

A. Center, patient, visit, and study identification

- 1. Center ID: ____ _____
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- **4.** Visit date (date this form is initiated):

day	mon	year

- **5.** Visit code: <u>r</u> <u>z</u> ____
- **6.** Form & revision: <u>r z 2</u>
- 7. Study: CyNCh <u>8</u>

B. Diabetes Status

8. In the judgment of the Study Physician and based on the patient's medical history and laboratory results, does the patient have diabetes:



9. Is the patient's diabetes poorly controlled (HbA1c greater than 9% within the past 90 days):



C. Alcohol use exclusions

10. Does the patient have a history of significant alcohol intake:



11. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her (past and current) alcohol intake:



12. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient's alcohol use since starting the screening process consistent with CyNCh eligibility criteria:



D. Laboratory test exclusions

- 13. Hepatic Decompensation
 - **a.** Is the patient's serum albumin less than 3.2 g/dL:



b. Is the patient's INR greater than 1.4:



c. Is the patient's direct bilirubin greater than 1.0 mg/dL:



d. Is the patient's total bilirubin greater than 3 mg/dL:



e. Is the patient's hemoglobin less than 10 g/dL:



f. Is the patient's white blood cell count less than 3,500 cells/mm³:



g. Is the patient's platelet count less than 130,000 cells/mm³:



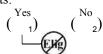
h. Is the patient's neutrophil count less than 1,500 cells/mm³:



i. Does the patient have a history of esophageal varices, ascites, or hepatic encephalopathy:



j. Tests are outside time window and clinic chose not to repeat tests:



E. Medication use exclusions

14. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the past 12 months:



15. Use of other known hepatotoxins within 90 days of liver biopsy or within 120 days of randomization:



16. Initiation of any new medication/vitamin or supplement to treat NAFLD/NASH in the time period following liver biopsy and prior to randomization:

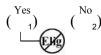


F. Other chronic liver disease exclusions

17. Does the patient have ongoing autoimmune liver disease defined by liver histology:



18. Does the patient have Wilson's disease defined by ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



19. Does the patient have alpha-1-antitrypsin (A1AT) genotype ZZ or SZ:



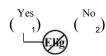
20. Does the patient have a transferrin saturation greater than 45% with histological evidence of iron overload (3+ or 4+ stainable iron on liver biopsy):



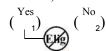
- **21.** Do any of the patient's assessments show evidence of other chronic liver disease
 - a. Suspected or proven liver cancer:



b. Hepatitis B (HBsAg):



c. Hepatitis C (HCV RNA or anti-HCV):

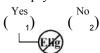


d. Any other type of liver disease other than NASH that warrants exclusion from the trial:



G. Liver biopsy exclusions

22. Inability to safely undergo a liver biopsy:



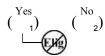
23. Biopsy out of window and patient chose not to repeat:



24. Biopsy inadequate for scoring and patient chose not to repeat:



25. Local pathologist did not find NAFLD:

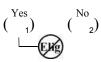


26. NAFLD activity score (NAS) less than 4:



H. Other medical exclusions

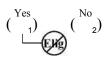
27. History of bariatric surgery or plans to have bariatric surgery during the CyNCh trial:



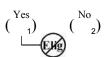
28. Inflammatory bowel disease (if active) or prior resection of small intestine:



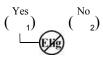
29. Active coagulopathy:



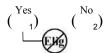
30. Active seizure disorders:



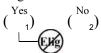
31. Gastrointestinal ulcers or other GI bleeding:



32. Renal dysfunction with a creatinine clearance of less than 90 mL/min/m²:



33. History of total parenteral nutrition (TPN) use in year prior to screening:



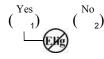
34. History of heart disease (myocardial infraction, heart failure, unstable arrhythmias):



35. Does the patient have clinically significant depression (patient was hospitialized for suicidal ideations or suicide attempts within the past 12 months):



36. History of active malignant disease requiring chemotherapy or radiation in the past 12 months prior to randomization:



37. Currently enrolled in a clinical trial or received an investigational study drug in the past 180 days:



38. Other conditions which, in the opinion of the investigator, would impede compliance or hinder completion of the study:



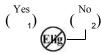
I. Birth control exclusion

39. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient (female of childbearing potential) willing to use effective birth control methods to avoid pregnancy during the 52 weeks of treatment (check "Yes" if patient is male or not of childbearing potential):



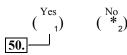
J. Check on ability to swallow study medication

40. In your judgment (Study Physician/Clinical Coordinator), is the patient able to swallow the CyNCh study medications (if you are unsure, you may ask the patient to swallow an empty capsule):



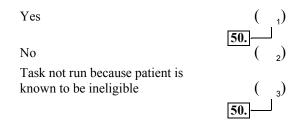
K. Eligibility check on day of randomization

41. Was an ineligibility condition checked or an eligibility not ascertained in items 9-40:



*Key forms RG, AD, BH, BP, CG, HF, LP, LR, LS, MR, ND, PE, PQ/PR, PW/PY, and SD. Run the Randomization Task on your clinic data system.

42. Were any stops or ineligible conditions other than "missing form RZ" identified by the Randomization Task:

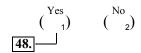


43. Based on today's physical examination, does the patient feel well today:

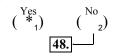


*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

44. Is the patient male:



45. Is the patient of childbearing potential:



*Administer pregnancy test.

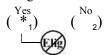
46. Is the patient pregnant (positive pregnancy test on the day of randomization):



*Go to item 50.

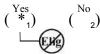
Patient ID).		

47. Is the patient currently breast feeding



*Go to item 50.

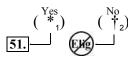
48. In the Study Physician's judgment, is there any reason to exclude the patient from randomization:



*If Yes, specify reason and then go to item 50:

specify reason

49. Does the patient still consent to randomization (you should ask the patient to orally affirm his/her consent):



*Go to item 51 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.

†Complete items 50 and 53-57 and key the form. The form must be keyed to document the reasons for ineligibility for CyNCh.

L. Reasons for ineligibility for ineligible patients

Note: Complete this section for ineligible patients only.

50. Reason for ineligibility (check all that apply)

a. Reason covered in items 9-4	19: (* ₁))
---------------------------------------	------------------------	---

b. Other reason not covered on this form *(specify):*



*Go to item 53

Μ.	Physical	Examination	(must be	done d	on the	day
	of randon	nization)				

- **51.** Height (shoes off)
 - **a.** 1st measurement:
 - **b.** 2nd measurement:
 - c. Units:

Inches (1

Centimeters (2

- **52.** Weight (With shoes off, weight should be obtained in pounds and kilograms using the scale. Do not calculate the weight conversions.)
 - a. Weight in pounds:

		•	
	lbs		

b. Weight in kilograms:

	•	
 kos		

c. Weight group:

Less than or equal to 65kg (

Greater than 65 - 80kg

Greater than 80kg (3

N. Administrative information

53. Study Physician PIN:

54. Study Physician signature:

55	Clinical Coordinator PIN:	

56.	Clinical	Coordinato	r signature:	

57. Date form reviewed

(Note: This form must be reviewed on the day of randomization; if it was keyed prior to the randomization day, update it, re-review it on the day of randomization, and key the revised date of review.):

day	mon	year

CyNCh

SD - Liver Biopsy Materials Documentation

Purpose: To document that the liver biopsy required for screening was obtained under the time and medication restrictions required by the protocol and to document whether liver tissue was obtained for banking (both screening and followup biopsies). The number and type of slides available for archival at the Data Coordinating Center are noted for both screening and followup biopsies. If slides cannot be archived at the Data Coordinating Center, the source of the slides and the time by which the slides must be returned to the clinical center are recorded.

When: Visits s, f52, and as needed for biopsies at interim times.

By whom: Clinical Coordinator in consultation with the Study Pathologist.

Instructions: This form provides information about the tissue and slides from the biopsy and alerts the DCC to expect completion of the Liver Tissue Banking (LT) form, receipt of tissue at the Biosample Repository, and receipt of slides from the biopsy at the Data Coordinating Center. It also provides a record of the source of the slides, the number and type of stained slides available for review at the clinical center, the need (if any) to borrow those stained slides or provision of those stained slides to the NASH CRN without requiring return of the slides, and the number of unstained slides to be provided to the NASH CRN. A copy of the original surgical pathology report for the biopsy must be obtained; the patient's name should be blacked out, the report should be annotated with the patient's NASH CRN ID number and code, and the annotated report should be stapled to the back of this form. The surgical pathology report documents the date of biopsy. The slides should be labeled using the labels provided by the DCC. For unstained slides use permanent labels with sequence numbers 01-60, the borrowed slides should be labeled with removable overlabels with sequence numbers 81-90.

A	Center.	natient	and	visit	iden	tification
A.	Cuitti,	patient	anu	4191t	iucii	uncanon

2. Patient ID:				
----------------	--	--	--	--

3.]	Patient	code:				
-------------	---------	-------	--	--	--	--

day	mon	year

5. Visit code:

				_
ĺ.	Form & revision:	S	d	- 1

B. Surgical pathology report

8. Is a copy of the report annotated with the patient's NASH CRN ID number and code and with name blacked out attached to this form:



* Obtain a copy of the report, annotate it, and attach it. You can use one of the pathology labels to annotate the report.

9. Biopsy information

a. Date of biopsy specified on the surgical pathology report:

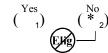
day	mon	year

b. Lobe specimen obtained from *(check only one):*

Right	(1.
Left	(2.
Unknown	(•

C. Requirements for screening biopsy

11. Is the date in item 9a within 120 days of the anticipated date of randomization:



* Biopsy date must be within 120 days of randomization.

D. Biopsy specimens and stained slides at the clinical center

12. Was a sample of liver tissue obtained for banking:

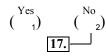
 $\binom{\text{Yes}}{*}_{1}$ $\binom{\text{No}}{2}$ * If Yes, complete the Liver Tissue Banking (LT)

13. What stained slides from the biopsy are available at the clinical center (check all that apply)

a. H & E stain:	(1)

E. Unstained slides to be sent to the DCC

14. Are unstained slides available for sending to the DCC:



- 15. How many unstained slides will be sent to the DCC: 01-10
- **16.** What are the slide sequence numbers for those slides (from the NASH CRN labels on each slide - use permanent labels, sequence numbers 01-60):

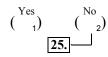
a. Slide sequence number	01-60
b. Slide sequence number	01-60
c. Slide sequence number	01-60
d. Slide sequence number	01-60

	01-00
e. Slide sequence number	
1	01-60
f. Slide sequence number	

F. Stained slides to be sent to the DCC

(The institution's stained slides must be sent to the DCC only if fewer than 3 unstained slides will be sent to the DCC)

17. Are any stained slides to be sent to the DCC:



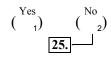
- 18. How many stained slides are to be sent to the DCC:
- **19.** Sequence number of slides to be sent to DCC
 - a. Slide sequence number of H & E stain:

	81-90	
on's		

- **b.** Slide sequence number of Masson's trichrome stain: 81-90
- **c.** Slide sequence number of iron stain:

d. Slide sequence number of other stain:

20. Are any stained slides to be returned to the clinic:



- 21. How many stained slides are to be returned to the clinic:
- 22. List sequence numbers of those slides to be returned
 - a. Slide sequence number:

81-90	
01 00	

b. Slide sequence number: c. Slide sequence number:

81-90	

d. Slide sequence number:

81-90	

23. When do the stained slides need to be returned to the clinical center (check only one):

Immediately after central review At the end of the NASH CRN funding period

(1)

24. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department

(1)
Other, (specify):

name

address

address

Note: this is the CyNCh trial record of the source of the slides i.e., where the clinical center should send the slides when they are received back from the DCC.

address

phone

\sim	A .1	• . • . 4	- 4.	·	4 •
J.	Aam	unistr	ative	inform	iatior

25. Clinical Coordinator PIN:

26. Clinical Coordinator signature:

27. Date form reviewed:

day mon year

SR - Serious Adverse Event/IND Safety Report

Purpose: To report serious adverse events recorded on the Adverse Event Report (AE) form that satisfy the FDA expedited FDA Safety Report requirements outlined in the CyNCh Trial protocol. In order to satisfy FDA expedited IND Safety Report requirements the event must be SERIOUS, UNEXPECTED, AND have a REASONABLE POSSIBILITY of being caused by CyNCh study drug, as defined by Title 21 Code of Federal Regulations Part 312.32 IND Safety Reporting:

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "SERIOUS" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "REASONABLE POSSIBILITY" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "**UNEXPECTED**" if it is not listed in the cysteamine bitartrase investigator's brochure or is not listed at the specificity or severity that has been observed for your patient.

When: The SR form should be used only for reporting a serious and unexpected adverse event which meets the IND Safety Report criteria as stated above, or when a followup report is needed for a previously completed SR form. When the serious adverse event does not meet the expedited IND Safety Report criteria, use the Advers Event Report (AE) form to report the event.

Completed by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form **within 2 business days**. The short name (item 24) and the severity grade (item 25) are to be obtained from the NCIs Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. (Click on Studies then click on CyNCh). Report the serious advere event to your IRB per local guidelines. Send the Data Coordinating Center the following:

- 1) A copy of this SR form and corresponding AE form
- 2) A narrative description of the event that includes all of the information provided on the SR and AE forms and a justification of why the event is serious, unexpected and has reasonable possibility of being caused by CyNCh study drug (see CyNCh SOP I, section 6.16).
- 3) A copy of your report to your IRB, if applicable

The Data Coordinating Center will submit a preliminary copy of the report to NIDDK (Sponsor) for further review within 3 business days. If NIDDK staff determines that an expedited IND Safety Report is required, a final report will be submitted to the FDA (within 15 days). Intercept Pharmaceuticals (manufacturer of study drug), the DSMB, and Steering Committee will be notified of all serious adverse events requiring an expedited IND safety report within 7 days of keying the SR form. For more information, see CyNCh SOP I, section 6.16.

Followup report: A followup report should be filed (use this form) when the adverse event is resolved or if there has been a significant change in the patients condition or in the physicians judgment about the event since the previous report was filed.

A. Center, patient and visit identification		4. Date of report:		
1. Center ID:			mon	year
2. Patient ID:		5. Visit code: If report not associated	d with a visit,	fill in ''n.''
3. Patient code:		6. Form & revision:	S	
		7. Study:	C	yNCh 8

B. Participant information

8. Date randomized in CyNCh:

day	mon	year

9. Gender:

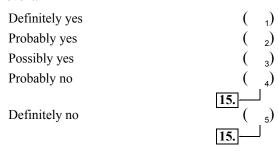
Male	(1)
Female	(2)

10. Age at time of adverse event:

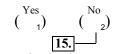
years

C. Determination of an serious adverse report

11. Is there a **reasonable possibility** that the CyNCh study drug caused the adverse event:

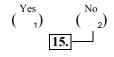


12. Is this adverse event **serious**:



If Yes, then select all the reasons that apply:

- **a.** Severity Grade 3, 4 or 5:
- **b.** Required inpatient hospitalization or prolonged existing hospitalization: (1)
- c. Persistent or significant incapacity or disruption of ability to conduct normal life functions:
- **d.** Jeopardized patient and required medical or surgical intervention: (1)
- e. Congenital anomaly or birth defect: (1
- **13.** Is this adverse event **unexpected**:



14. Reason the adverse event was unexpected:

Not listed in the cysteamine bitartrate investigator brochure

(1)

Listed in the cysteamine bitartrate investigator's brochure, but not at the specificity or severity that has been observed

(₂)

Listed in the cysteamine bitartrate investigator's brochure as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with previous experience of cysteamine bitartrate

(3)

15. Did you select "Yes" for items 11, 12, and 13:

1	Yes	No
(*,)	(\dagger_2)
(17	(2)

*NIDDK will determine if an expedited IND Safety Report will be submitted to the FDA within 15 calendar days.

†Use CyNCh forms AE form to report adverse events that are not serious, not associated with the CyNCh study drug, or are expected. Do not key this form.

D. Serious adverse event description

16. Is this the first report or a followup report for this serious adverse event:

First report

 $\begin{pmatrix} 1 \end{pmatrix}$

Followup report

 $\begin{pmatrix} & & \\ & 2 \end{pmatrix}$

17. Date of serious adverse event onset:

=		_
day	mon	year

18. Date serious adverse event was reported to clinical center:



19. Describe the serious adverse event:

20.	Medications or supplements other than CyNCh study drug in use at the time of serious adverse event:	25. Severity grade (severity grades are listed CTCAE v3.0 document availa www.nashcrn.com; click on Studies and the on CyNCh):	b l e	e at
		Grade 3 - Severe	(1)
		Grade 4 - Life threatening or disabling	(2)
		Grade 5 - Death	(*3)
		*Complete and key the Death Report (DR)) foi	-
21.	Specify tests/treatments and comorbidities:	26. Did the serious adverse event result in any of the following <i>(check all that apply)</i>	ı	
		a. Emergency department/urgent care visit:	(₁)
		b. Hospital admission or prolonged hospital stay:	(1)
		c. Significant or persistent disability:	(1)
		d. Congenital anomaly or birth defect:	(1)
••		e. Death (complete and key CyNCh DR form):	(1)
22.	Was an unscheduled liver biopsy performed:	f. Other significant hazard or harm:	(1)
	$\begin{pmatrix} \text{Yes} & \begin{pmatrix} \text{No} \\ *_1 \end{pmatrix} & \begin{pmatrix} \text{No} \\ *_2 \end{pmatrix} \end{pmatrix}$			
	*Attach a copy of the institutional pathology report to the SR form.			
23.	Did the serious adverse event result in significant sequelae:	g. None of the above	(1)
	$\begin{pmatrix} \text{Yes} \\ 1 \end{pmatrix} \qquad \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$	27. Current status of serious adverse event <i>(check only one):</i>		
	24.	Resolved	(1)
	Specify:	Active	(2)
		Unknown	<u>-</u> (_ _ ₃)
		29. Data masalus di	<u>.</u>]—	_
		28. Date resolved:		
24.	Short name for serious adverse event (short names for AEs are listed in the CTCAE v3.0 document available	day mon	year	
	at www.nashcrn.com; click on Studies and then click on CyNCh):	29. Additional comments on serious adverse event:		

Patient ID:	 	
ration ii.		

E. Administrative informat

30.	Study Physician PIN:
31.	Study Physician signature:
32.	Clinical Coordinator PIN:
33.	Clinical Coordinator signature:
34.	Date form reviewed:

Key this form and send the DCC within 2 business days:

mon

year

(1) A copy of this SR form

day

- (2) A narrative description of the serious adverse event
- (3) A copy of your report to your IRB.

We are asking for copies of these reports on serious adverse events so that we assure appropriate and timely study wide review. The serious adverse event report will be reviewed by Dr. Jeanne Clark, the Safety Officer, and NIDDK (Sponsor).

Transfer Notification

Purpose: To record a transfer from one center to another center.

When: Upon transferring to the enrolling center and prior to the first visit at the adopting center.

By whom: Clinical coordinator of each center (enrolling center: sections A-C, adopting center: sections D- E).

Instruction: For enrolling center: When patient notifies enrolling center of upcoming transfer, the enrolling clinical coordinator should (1) complete Sections A-C of the Transfer Notification (TN Form), (2) send the TN form to the adopting center, with a copy of the most recently completed FH, LR, RD, and PE/PF forms, (3) send the labels for cryovials and slides and a copy of the visit window schedule to the adopting center. **For adopting center:** Prior to the patient coming to the adopting center, the adopting clinical coordinator should: (1) complete Sections D-E of the TN form, (2) Fax the TN form to the DCC (Fax: 410-955-0543). The DCC will key the form.

A. Enrolling center and patient identification	 D. Adopting center, patient and visit identification 14. Adopting center ID:			
1. Center ID:				
2. Patient ID:				
3. Patient code:4. Date of notification of intent to transfer:				
	17. Expected date of first follow-up visit at adopting center:			
6. Form & revision: t n 1	day mon year			
7. Study: CyNCh 8	18. Visit ID code for expected first follow-up visit at adopting center: f			
B. Last follow-up visit information8. Date of last follow-up visit:	Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.			
day mon year	E. Adopting center administrative information			
9. Visit ID code of last completed follow-up visit: _f	19. Date form reviewed:			
10. Have cryovial and slide labels been sent to the adopting center: Yes No	day mon year 20. Clinical coordinator ID:			
*Send the cryovial and slide labels to the adopting center (using a package tracking service).	21. Clinical coordinator signature:			
C. Enrolling center administrative information	Fax form to the DCC. The DCC will key the TN form.			
11. Date form reviewed:				
day mon year				
12. Clinical coordinator ID:				
13. Clinical coordinator signature:				