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
AE	Adverse Event Report
AN	Serious Adverse Event Report
BC	Blood Collection for DNA
BD	Food Questionnaire Documentation
BG	Baseline History
BH	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 – 1st Reading
HT	Steatohepatitis Determination –2nd 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)

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

c r 3 6. Form and revision

__ 7. Study: **6**=Database 2

__ __ / __ __ __ / __ __ 8. Date of biopsy

B. Slide sequence number

9. 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 (*Specify*):

D. Histology

_____ *Patient ID*

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

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 (*does not require trichrome*); **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

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: d r 2

7. Study: NAFLD Database 2 6

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Other caregiver: (1)
d. Health care provider or NASH CRN staff: (1)
e. Newspaper: (1)
f. Funeral parlor/home: (1)
g. Medical record: (1)
h. Medical examiner: (1)
i. Coroner: (1)
j. National Death Index (NDI): (1)
k. Social Security Death Master File (SSDMF): (1)
l. Other *(specify):* (1)

_____
other source

_____
other source

10. Place and location of death

a. Place of death *(check only one):*

Hospital (1)
Hospice (2)
Home (3)
Nursing home (4)
Other *(specify):* (5)

_____

Unknown (6)

b. Location of death:

_____
city/state/country

11. Has a death certificate been obtained:

Yes (1) No (2)

If no, please obtain or explain why not:

_____

_____

_____

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

Coronary heart disease (01) **13.**

Cardiovascular disease (02) **14.**

Liver disease (03) **15.**

Malignancy (cancer) (04) **16.**

Gastrointestinal (GI) disease (05) **17.**

Pulmonary (lung) disease (06) **18.**

Pneumonia (07) **19.**

Complication of diabetes (08) **19.**

Accident (09) **19.**

Suicide (10) **19.**

Homicide (11) **19.**

Kidney disease or renal failure (12) **19.**

Sepsis, staph or other infection (13) **19.**

Multi-organ failure (14) **19.**

Other *(specify):* (15) **19.**

_____

Unknown (16) **19.**

13. CAUSE OF DEATH: Coronary heart disease (CHD) subclassification ***(check only one)***:

Definite fatal myocardial infarction (MI) or heart attack (1)

Defined as:
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 (3)

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 (2)

Defined as: Death due to brady- or tachy- arrhythmias not associated with an acute ischemic event.

Cerebrovascular (stroke) (3)

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

Other cardiovascular (4)

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

Specify: _____

Go to 19.

15. CAUSE OF DEATH: Liver disease subclassification ***(check only one)***:

- Nonalcoholic fatty liver disease (NAFLD) (1)
- Chronic hepatitis C (2)
- Acute liver failure (3)
- Other *(specify):* (4)

_____

19. ___

16. CAUSE OF DEATH: Malignancy (cancer) subclassification ***(check only one)***:

- Breast cancer (01)
- Colon cancer (02)
- Endometrial/Uterine cancer (03)
- Esophageal cancer (04)
- Hepatocellular carcinoma (HCC)* (05)
  * *Complete and key the HC form.*
- Ovarian cancer (06)
- Pancreatic cancer (07)
- Prostate cancer (08)
- Rectal cancer (09)
- Other known cancer or malignant tumor *(specify):* (10)

_____

- Unknown cancer site (11)

19. ___

17. CAUSE OF DEATH: Gastrointestinal subclassification ***(check only one)***:

- Diverticular disease (1)
- *Clostridium difficile* colitis (2)
- Intestinal obstruction (3)
- Ulcer *(gastric, duodenal, peptic, gastrojejunal)* (4)
- Vascular disorders of the intestine (5)
- Other *(specify):* (6)

_____

19. ___

18. CAUSE OF DEATH: Pulmonary (lung) subclassification ***(check only one)***:

- Asthma (1)
- Acute respiratory failure (2)
- Interstitial lung disease (ILD) (3)
- Other *(specify):* (4)

_____

19. Contributing causes of death ***(check all that apply)***:

- **a.** Coronary heart disease (CHD) *(specify):* (1)

_____

- **b.** Cerebrovascular disease (stroke): (1)
- **c.** Congestive heart failure (CHF): (1)
- **d.** Documented arrhythmia, not associated with MI: (1)
- **e.** Other cardiovascular disease *(specify):* (1)

_____

- **f.** Diabetes Type 1: (1)
- **g.** Diabetes Type 2: (1)
- **h.** Liver disease *(specify):* (1)

_____

- **i.** Hepatocellular (liver) carcinoma (HCC)*: (1)
  * *Complete and key the HC form.*
- **j.** Other malignancy (cancer) *(specify):* (1)

_____

- **k.** Gastrointestinal (GI) disease *(specify):* (1)

_____

- **l.** Pulmonary (lung) disease *(specify):* (1)

_____

- **m.** Pneumonia: (1)
- **n.** Kidney disease: (1)
- **o.** Sepsis, staph or other infection: (1)
- **p.** Other *(specify):* (1)

_____

- **q.** Unknown: (1)
- **r.** None: (1)

20. Was this a procedure-related death:

Yes (1) No (2)

→ **22.**

21. Type of procedure-related death ***(check only one)***:

Cardiac death: Cardiovascular-related procedure
(Defined as death after invasive cardiovascular intervention. Death within 28 days of cardiovascular surgery or within 7 days of cardiac cath, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary vascular intervention.): (1)

Cardiac death: Noncardiovascular procedure
(Defined as cardiac death after noncardiovascular intervention which occurs within 28 days of surgery or other invasive procedure.): (2)

Non-cardiac death (3)

Unknown (4)

22. Was an autopsy performed ***(check only one)***:

Yes (1)

No (2)

Unknown (3)

23. Documentation available for future formal death adjudication ***(check all that 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 (1)

Narrative is not included (2)

If not, please explain why not:

_____

_____

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 year

Narrative - do not key:

NAFLD Database 2

FR - FibroScan® Report

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 FibroScan® exam):*

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: f r 5

7. Study: NAFLD Database 2 6

B. Consent

8. Has the patient signed the FibroScan® consent:

Yes (1) No (*2)

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.: (1)

b. Wound near the site of scan: (1)

c. Pregnancy: (1)

d. Ascites (fluid in the abdomen): (1)

e. Patient did not fast for 3 hours: (1)

f. Were any of the items above (a-e) checked:

Yes (*1) No (2)

21. ____

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

C. FibroScan® Procedure information

10. Was FibroScan® exam performed:

Yes (1) No (* 2)

12.

** Complete item 11, then skip to item 21.*

11. Reason FibroScan® exam not performed *(check all that apply):*

a. Patient had a skin-to-capsule distance measurement greater than 3.5cm: (1)

b. Other *(specify):* (1)

_____

Skip to item 21.

12. Probe type used:

M: (1)

XL: (2)

D. FibroScan® exam #1 results

13. FibroScan® Technician PIN: ____ ____ ____

14. Number of measurements

a. Valid measurements*: ____ ____ # of valid measurements

b. Invalid measurements: ____ ____ # of invalid measurements

c. Total measurements: ____ ____ # of total measurements

To calculate invalid measurements, subtract valid measurements from total measurements

** Note: at least ten valid measurements should be made.*

15. Equivalent Liver Stiffness (E)

a. Median (kPa): ____ ____ ____ • ____ (1.5-75.0)

b. IQR (kPa): ____ ____ ____ • ____

c. IQR/med: ____ ____ %

16. Controlled Attenuation Parameter (CAP)

a. Median (dB/m): ____ ____ ____ (100-400)

b. IQR (dB/m): ____ ____ ____

E. FibroScan® exam #2 results

(This may be done by the same technician or a different technician).

17. FibroScan® Technician PIN: ____ ____ ____

18. Number of measurements

a. Valid measurements*: ____ ____ # of valid measurements

b. Invalid measurements: ____ ____ # of invalid measurements

c. Total measurements: ____ ____ # of total measurements

To calculate invalid measurements, subtract valid measurements from total measurements

** Note: at least ten valid measurements should be made.*

19. Equivalent Liver Stiffness (E)

a. Median (kPa): ____ ____ ____ • ____ (1.5-75.0)

b. IQR (kPa): ____ ____ ____ • ____

c. IQR/med: ____ ____ %

20. Controlled Attenuation Parameter (CAP)

a. Median (dB/m): ____ ____ ____ (100-400)

b. IQR (dB/m): ____ ____ ____

F. Administrative information

21. Study Physician PIN: ____ ____ ____

22. Study Physician signature:

_____

23. Clinical Coordinator PIN: ____ ____ ____

24. Clinical Coordinator signature:

_____

25. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

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:

Yes (1) No (*2)

17.

B. Consent

9. Has the patient signed the FLINT MRI consent:

Yes (1) No (*2)

17.

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

C. MRI results and information

10. Was an MRI performed:

Yes (1) No (*2)

12.

** Complete item 11, then skip to item 17.*

11. Reason MRI not performed *(check all that apply)*

a. Patient was not fasting: (1)

b. Patient suffers from extreme claustrophobia: (1)

c. Patients weight or girth exceeds MRI scanner capabilities: (1)

d. Other *(specify):* (1)

_____

17.

12. Technician name:

_____
print name

13. Date and time of MRI:

____ ____–____ ____ ____–____ ____
day mon year

a. Time:

____ ____ : ____ ____ (1) am (2) pm
hour minute

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: n ____ ____ ____

6. Form & revision: h c 1

7. Study: NAFLD Database 2 6

B. Diagnosis information

8. Date of diagnosis:

____ ____–____ ____ ____–____ ____
day mon year

9. How was HCC identified *(check all that apply):*

a. Ultrasound: (1)
b. CT scan: (1)
c. MRI: (1)
d. Biopsy: (1)
e. Other *(specify):* (1)

_____

10. Were results of imaging obtained:

Yes (1) No (2)
15.

11. Were multiple tumors identified:

Yes (1) No (2)

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

____ ____ . ____
cm

13. Was early enhancement present:

Yes (1) No (2)

14. Was delayed washout present:

Yes (1) No (2)

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

Yes (1) No (2)
16.

a. Was serum AFP elevated: Yes (1) No (2)

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:

____ ____–____ ____ ____–____ ____
day mon year

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code:

n ____ ____ ____

6. Form & revision: i e 3

7. Study: NAFLD Database 2 6

B. Visit interval identification

8. Most recently completed visit (screening or follow-up)

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____ ____

C. Patient information

9. Date enrolled in NAFLD Database 2 Study *(enter n if patient is not yet enrolled):*

____ ____–____ ____ ____–____ ____
day mon year

10. Gender:

Male (1)
Female (2)

11. Age at time of event: ____ ____
years

D. Event description

12. Date event started:

____ ____–____ ____ ____–____ ____
day mon year

13. Nature of event *(check all that apply)*

a. General anesthesia (1)
b. Study-related procedure: (1)
c. Drug interactions: (1)
d. Worsening of a co-morbid illness: (1)
e. Hypoglycemia: (1)
f. New-onset diabetes: (1)
g. Pregnancy *(patient):* (1)
h. Cirrhosis: (1)
i. Hepatocellular carcinoma (HCC): (* 1)
** Complete and key the HC form.*
j. Other *(specify):* (1)

_____

_____

14. Did the event lead to *(check all that apply)*

a. Emergency room visit: (1)

b. Hospitalization: (1)

c. Infectious episode: (1)

d. Surgical intervention: (1)

15. Describe event:

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*):

Yes (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):

17. Indicate the severity code using the CTCAE grading scale for the AE specified (*severity grades are listed in the CTCAE v3.0 document available at https://jhuccs1.us/nash/default.asp; click on Documents and then click on General Documents*):

Grade 1 - Mild (1)

Grade 2 - Moderate (2)

Grade 3 - Severe† (3)

Grade 4 - Life threatening or disabling† (4)

Grade 5 - Death† (* 5)

†*Fax the DCC (Attention Pat Belt) a copy of this form if severity grade is 3 or higher (Fax 410-955-0932).*

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

18. Date event resolved
(enter n if event is not yet resolved):

____ ____–____ ____ ____–____ ____
day mon year

19. What action was taken:

20. Other comments on event:

F. Administrative information

21. Clinical Coordinator PIN: ____ ____ ____

22. Clinical Coordinator signature:

23. Study Physician PIN: ____ ____ ____

24. Study Physician signature:

25. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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.

FLINT

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____
if report not associated with a visit, fill in ''n''

6. Form & revision: i e 3

7. Study: FLINT 7

B. Visit interval identification

8. Most recently completed visit (screening or followup)

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____

C. Patient information

9. Gender:

Male (1)
Female (2)

10. Age at time of event: ____ ____
years

D. Event description

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

First report (1)
Followup report (2)

12. Date event started:

____ ____–____ ____ ____–____ ____
day mon year

13. Nature of event *(check all that apply)*

a. Drug dispensing mixup: (1)
b. Medication related event: (1)
c. Study procedure related event: (1)
d. Severe allergic reaction: (1)
e. Drug interactions: (1)
f. Worsening of a co-morbid illness: (1)
g. Patient reported symptom of hepatotoxicity: (1)
h. Hypoglycemia/hyperglycemia: (1)
i. Diabetes: (1)
j. Pregnancy *(patient):* (*1)
k. Other *(specify):* (1)

_____

_____

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

14. Describe event:

_____

_____

_____

_____

_____

_____

For items 15, 16, and 17, please refer to CTCAE v3.0 available at www.nashcrn.com; click on Studies and then FLINT.

15. Identify body system *(check all that apply)*

a. Auditory/ear: (1)
b. Allergy/immunologic: (1)
c. Ocular/visual: (1)
d. Hepatobiliary/pancreatic: (1)
e. Infection: (1)
f. Constitutional symptoms: (1)
g. Psychiatric: (1)
h. Cardiovascular: (1)
i. Dermatologic/skin: (1)
j. Endocrine/metabolic: (1)
k. Gastrointestinal/digestive: (1)
l. Lymphatic/blood: (1)
m. Musculoskeletal: (1)
n. Neurologic: (1)
o. Pulmonary/respiratory: (1)
p. Renal/genitourinary: (1)
q. Sexual/reproductive: (1)
r. Other *(specify):* (1)

_____
specify other body system

s. None of the above: (1)

16. Short name for event if applicable:

Not applicable (0)

_____

_____

17. 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	(4)
Grade 5 - Death	(*5)

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

18. Randomization in FLINT

a. Has patient been randomized in FLINT:

(Yes 1) (No 2)

26.

b. Date randomized in FLINT:

____ ____–____ ____ ____–____ ____
day mon year

19. Is the patient currently receiving the FLINT study drug:

(Yes 1) (No 2)

20. Patient's history of treatment with FLINT study drug

a. How long has patient been on study drug:

_____

b. Have there been any treatment interruptions or restarts:

(Yes 1) (No 2)

Include stop/restart dates and reasons:

_____

_____

_____

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

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

22. Is this a serious adverse event:

(Yes 1) (No 2)

23.

If Yes, then select all the reasons that apply:

a. Severity Grade 4 or 5: (1)

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: (1)

e. Congenital abnormality or birth defect: (1)

23. Is this an unexpected adverse event:

(Yes 1) (No 2)

25.

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	(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:

(Yes *1) (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	(3)

28.

28.

27. Date adverse event resolved:

____ ____–____ ____ ____–____ ____
day mon year

28. What action was taken:

29. Other comments on event:

E. Administrative information

30. Clinical Coordinator PIN: ____ ____ ____

31. Clinical Coordinator signature:

32. Study Physician PIN: ____ ____ ____

33. Study Physician signature:

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.

FLINT

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____
If report not associated with a visit, fill in ''n.''

6. Form & revision: s r 3

7. Study: FLINT 7

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 (2)
Possibly yes (3)
Probably no (4)
15.
Definitely no (5)
15.

12. Is this a serious adverse event:

Yes (1) No (2)
15.

If Yes, then select all the reasons that apply:

a. Severity Grade 4 or 5: (1)

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: (1)

e. Congenital abnormality or birth defect: (1)

13. Is this an unexpected adverse event:

Yes (1) No (2)
15.

14. Reason the adverse event was unexpected:

Not listed in the obeticholic acid investigator brochure (1)

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

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

Yes (*1) No (†2)
STOP

**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 (1)
Followup report (2)

17. Date of serious adverse event onset:

____ ____–____ ____ ____–____ ____
day mon year

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

____ ____–____ ____ ____–____ ____
day mon year

19. Describe the serious adverse event:

20. Medications or supplements other than FLINT study drug in use at the time of serious adverse event:

_____

_____

_____

_____

_____

21. Specify tests/treatments and comorbidities:

_____

_____

_____

_____

_____

22. Was an unscheduled liver biopsy performed:

(Yes *1) (No 2)

**Attach a copy of the institutional pathology report to the SR form.*

23. Did the serious adverse event result in significant sequelae:

(Yes 1) (No 2)

24.

Specify:

_____

_____

_____

_____

24. Short name for serious adverse event *(short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Studies and then click on FLINT):*

_____

_____

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 (*3)

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

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

Resolved (1)

Active (2)

28.

Unknown (3)

28.

27. Date resolved:

____ ____–____ ____ ____–____ ____
day mon year

28. Additional comments on serious adverse event:

_____

_____

_____

_____

E. Administrative information

29. Study Physician PIN: ____ ____ ____

30. Study Physician signature:

_____

31. Clinical Coordinator PIN: ____ ____ ____

32. Clinical Coordinator signature:

_____

33. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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

(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).

NAFLD Database 2

BG - Baseline History

Purpose: To collect baseline history information about the patient.
When: Visit t0.
Administered by: Clinical Coordinator, reviewed by Study Physician.
Respondent: Patient or patient's parent.
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 NAFLD Database 2 Study. If ⊘EXC is checked for an item, the patient is ineligible and cannot enroll in the NAFLD Database 2 Study. 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.

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 0 ____ ____

6. Form & revision: b g 2

7. Study: NAFLD Database 2 6

B. Family history

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

(Yes 1) (No 2)

10.

a. Did any of the patient's first degree relatives die from liver disease:

(Yes 1) (No 2)

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

a. Alcohol related liver disease: (1)
b. Viral hepatitis: (1)
c. Alpha-1 antitrypsin deficiency: (1)
d. Wilson's disease: (1)
e. Glycogen storage disease: (1)
f. Iron overload: (1)
g. Fatty liver disease *(NAFLD, NASH):* (1)
h. Type of liver disease unknown: (1)
i. Other *(specify):* (1)

_____
specify

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

(Yes 1) (No 2)

12.

11. If yes, is the cause of the cirrhosis NASH-related or unknown (cryptogenic):

(Yes 1) (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)

14. Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:

Yes (1)
No (2)
Don't know (3)

15. Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood fat:

Yes (1)
No (2)
Don't know (3)

C. NAFLD history

16. Date patient was first diagnosed with fatty liver disease or NASH-related cirrhosis:

____ ____–____ ____ ____–____ ____
day mon year

17. What prompted the evaluation for NAFLD, NASH, or NASH-related cirrhosis *(check all that apply)*

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)
e. Other *(specify):* (1)

_____
specify

18. What procedures/tests supported this first diagnosis *(check all that apply)*

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

_____
specify

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 evaluated for the Database 2 Study *(complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy):*

Yes (*1) No (2)
21.

**Blood drawn for specimen collection must be within 90 days of the biopsy.*

20. Date of liver biopsy no more than 90 days prior to registration in Database 2 Study that you want evaluated:

____ ____–____ ____ ____–____ ____
day mon year

21. Will the patient have a biopsy during screening:

Yes (*1) No (2)

**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 4 days after the biopsy.*

22. Has the patient had a liver imaging study in the past 6 months:

Yes (*1) No (2)

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

D. Weight history

23. What was the patient's birthweight:

____ ____–____ ____
lbs oz

24. *Review flashcard 11.* 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)
No or minimal change (6)

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

28. Is the patient age 18 or older:

Yes (1) No (2)
31.

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

____ ____ ____
lbs

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:

Yes (1) No (2)
33.

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

____ ____ ____
lbs

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

Yes (1) No (2)
35.

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:

Yes (1) No (2)
37.

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 12 or older:

Yes (1) No (2)
43.

38. Have you ever smoked tobacco cigarettes:

Never (1)
43.
In the past but not anymore (2)
Currently smokes cigarettes (3)

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):*

Yes (1) No (2)
43.

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

____ ____
years

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

____ ____
years

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

____ ____ ____
cigarettes/day

F. Menstrual history

43. Is the patient female:

(Yes 1) (No 2)

49.

44. Has menarche occurred:

(Yes 1) (No 2)

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:

(Yes 1) (No 2)

49.

48. 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 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: (1)

b. Diabetes type 2: (1)

c. Gestational diabetes *(diabetes of pregnancy):* (1)

d. Hepatitis B: (1) C

e. Hepatitis C: (1) C

f. Autoimmune hepatitis: (1)

g. Autoimmune cholestatic liver disorder (PBC or PSC): (1) C

h. Wilson's disease: (1) C

i. Alpha-1-antitrypsin (A1AT) deficiency: (1) C

j. Glycogen storage disease: (1) C

k. Iron overload: (1) C

l. Polycystic liver disease: (1)

m. Drug induced liver disease: (1)

n. Gilbert's syndrome: (1)

o. Esophageal or gastric varices on endoscopy: (1)

p. Bleeding from varices: (1)

q. Other gastrointestinal bleeding: (1)

r. Ascites: (1)

s. Edema: (1)

t. Hepatic encephalopathy: (1)

u. Portal hypertension: (1)

v. Hepatorenal syndrome: (1)

w. Hepatopulmonary syndrome: (1)

x. Short bowel syndrome: (1) C

y. Hemophilia *(bleeding disorder):* (1) C

z. HIV positive: (1) C

aa. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

ab. Endocrine disease *(hormonal abnormality):* (1)

ac. Hepatocellular carcinoma: (1) C

ad. Other malignancy *(cancer):* (1)

ae. Peripheral neuropathy: (1)

af. Seizure disorder or epilepsy: (1)

ag. Drug allergies: (1)

ah. Hypothyroidism: (1)

ai. Hypertension: (1)

aj. Cerebrovascular disease: (1)

ak. Dysbetalipoproteinemia: (1)

C

al. Chronic cholestasis: (1)

am. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

an. Pancreatitis: (1)

ao. Cholelithiasis: (1)

ap. Coronary artery disease: (1)

aq. Elevated uric acid such as gout: (1)

ar. Kidney disease: (1)

as. Polycystic ovary syndrome: (1)

at. Sleep apnea *(not breathing during sleep):* (1)

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (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 any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1)

C

b. Jejunoileal *(or other intestinal)* bypass prior to the diagnosis of NAFLD: (1)

C

c. Biliopancreatic diversion: (1)

C

d. Other GI or bariatric surgery *(specify):* (1)

_____

e. None of the above: (1)

51. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) No (2)

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

Yes (1) No (2)

52. Has the patient received total parenteral nutrition (TPN) for more than 1 month within 6 months prior to liver biopsy:

Yes (1) No (2)

F,Hg

53. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) No (2)

54. Does the patient have symptoms suggestive of sleep apnea *(snoring, observed periods of apnea, disruptive sleep disturbances):*

Yes (1) No (2)

H. Medication use

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

Yes (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, Glucotrol XL): (1)
f. Glyburide (Micronase, DiaBeta, Glynase): (1)
g. Insulin: (1)
h. Metformin (Glucophage, Glucophage XR): (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)

_____

56. Has the patient taken any alcohol abuse (dependance or withdrawal) medications in the past 3 months:

Yes (1) No (2) **57.**

(If 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)

_____

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

Yes (1) No (2) **58.**

(If yes, check all that apply):

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

_____

58. Has the patient taken any antiobesity medications in the past 3 months:

Yes (1) No (2) **59.**

(If yes, check all that apply):

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

_____

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

Yes (1) No (2) **60.**

(If yes, 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. Other, *(specify):* (1)

_____

j. Other, *(specify):* (1)

_____

60. Has the patient taken any strong opiates containing acetaminophen medication in the past 3 months:

Yes (1) No (2) **61.**

(If yes, check all that apply):

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

_____

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

Yes (1) No (2) **62.**

(If yes, 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)

_____

62. Has the patient taken any anticoagulant/antiplatelet medications in the past 3 months:

Yes (1) No (2) **63.**

(If yes, 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)

_____

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

( ) Yes ( ) No

64.

(If yes, check all that apply):

a. Betamethasone sodium (Celestone): ( )

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):* ( )

_____

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

( ) Yes ( ) No

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): ( )

l. Furosemide (Lasix): ( )

m. Hydrochlorothiazide (Esidrix, HydroDIURIL): ( )

n. Hydrochlorothiazide + triamterene (Dyazide): ( )

o. Lisinopril (Prinivil, Zestril): ( )

p. Losartan potassium (Cozaar): ( )

q. Losartan potassium with hydrochlorothiazide (Hyzaar): ( )

r. Metoprolol (Lopressor): ( )

s. Nifedipine (Adalat, Procardia): ( )

t. Perhexiline maleate: ( )

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):* ( )

_____

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

Yes (1) No (2)

66.

(If yes, check all that apply):

a. Conjugated estrogen (Premarin/Prempro): (1)

b. Diethylstilbestrol and methyltestosterone (Tylosterone): (1)

c. Esterified estrogen (Estratab, Menest): (1)

d. Estradiol (Estrace): (1)

e. Ethinyl estradiol (Estinyl): (1)

f. Fluoxymesterone (Android-F, Halotestin): (1)

g. Levonorgestrel (Norplant): (1)

h. Medroxyprogesterone (Cycrin, Provera): (1)

i. Megestrol (Megace): (1)

j. Methyltestosterone (Android): (1)

k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): (1)

l. Norethindrone (Micronor): (1)

m. Norgestrel (Ovrette): (1)

n. Oral contraceptives: (1)

o. Oxandrolone (Oxandrin): (1)

p. Oxymetholone (Anadrol): (1)

q. Progesterone (Prometrium): (1)

r. Raloxifene (Evista): (1)

s. Tamoxifen (Nolvadex): (1)

t. Other, *(specify):* (1)

_____

u. Other, *(specify):* (1)

_____

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

Yes (1) No (2)

67.

(If yes, check all that apply):

a. Beclomethasone dipropionate (Beclovent, Vanceril): (1)

b. Budesonide (Pulmicort, Rhinocort): (1)

c. Fluticasone propionate (Flonase, Flovent): (1)

d. Loratadine (Claritin): (1)

e. Mometasone furoate (Nasonex): (1)

f. Triamcinolone acetonide (Azmacort, Nasacort): (1)

g. Other, *(specify):* (1)

_____

h. Other, *(specify):* (1)

_____

67. Has the patient taken a multivitamin regularly in the past 3 months:

Yes (1) No (2)

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

Yes (1) No (2)

70.

69. Which vitamins has the patient taken *(check all that apply):*

a. Vitamin B (any type): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Vitamin E: (1)

e. Other, *(specify):* (1)

_____

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

Yes (1) No (2)

71.

(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): (1)
i. Cod liver oil: (1)
j. Coenzyme Q: (1)
k. Dichloroacetate: (1)
l. 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)

_____

ad. Other, *(specify):* (1)

_____

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

Yes (1) No (2)

72.

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

a. Demeclocycline (Declomycin): (1)
b. Divalproex (Depakote): (1)
c. Doxycycline (Monodox): (1)
d. Isotretinoin (Accutane): (1)
e. Levothyroxine (Levoxyl, Synthroid): (1)
f. Liothyronine (Cytomel): (1)
g. Methotrexate (Rheumatrex): (1)
h. Minocycline (Dynacin, Minocin): (1)
i. Oxytetracycline (Terramycin): (1)
j. Penicillamine (Cuprimine, Depen): (1)
k. Tetracycline (Achromycin): (1)
l. Trientine hydrochloride (Syprine): (1)
m. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)
n. Valproate sodium (Depacon): (1)
o. Valproic acid (Depakene): (1)
p. Other, *(specify):* (1)

_____

q. Other, *(specify):* (1)

_____

r. Other, *(specify):* (1)

_____

I. Administrative information

72. Study Physician PIN: ____ ____ ____

73. Study Physician signature:

_____

74. Clinical Coordinator PIN: ____ ____ ____

75. Clinical Coordinator signature:

_____

76. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database 2

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: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: i r 1

7. Study: NAFLD Database 2 6

B. Upper abdominal ultrasound

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

Yes (1) No (2)

11.

9. Date of most recent upper abdominal ultrasound:

____ ____–____ ____ ____–____ ____
day mon year

10. 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. Intrahepatic biliary dilatation: (1)
f. Extrahepatic biliary dilatation: (1)
g. Gallstones/cholelithiasis: (1)
h. Gall bladder polyps: (1)
i. Cholecystectomy: (1)
j. Splenomegaly: (1)
k. Ascites: (1)
l. Other features of portal hypertension *(specify):* (1)

_____

_____

m. Other abnormality *(specify):* (1)

_____

_____

n. None of the above: (1)

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)*:

(Yes 1) (No 2)

14.

12. Date of most recent upper abdominal CT scan:

____ ____–____ ____ ____–____ ____
day mon year

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

_____

_____

o. Other abnormality *(specify):* (1)

_____

_____

p. None of the above: (1)

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)*:

(Yes 1) (No 2)

17.

15. Date of most recent upper abdominal MRI:

____ ____–____ ____ ____–____ ____
day mon year

16. 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. Splenomegaly: (1)
j. Ascites: (1)
k. Other features of portal hypertension *(specify):* (1)

_____

_____

l. Other abnormality *(specify):* (1)

_____

_____

m. None of the above: (1)

E. Administrative information

17. Study Physician PIN: ____ ____ ____

18. Study Physician signature:

_____

19. Clinical Coordinator PIN: ____ ____ ____

20. Clinical Coordinator signature:

_____

21. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NASH CRN NAFLD Database

NAFLD Database Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
AN	Serious Adverse Event Report
BC	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
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
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

NAFLD Database

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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: **s 1** _____ _____

6. Form & revision: **a d 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient (1)
→ **10.**

Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that 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

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)

→ **22.**

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?

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

15. 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
(0)	(1)	(2)	(3)	(4)

16. 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
(0)	(1)	(2)	(3)	(4)

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?

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

18. 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
(0)	(1)	(2)	(3)	(4)

19. 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
(0)	(1)	(2)	(3)	(4)

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

No	Yes, but not in the last year	Yes, during the last year
(0)	(1)	(2)

21. 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
(0)	(1)	(2)

22. Today's date:

_____

Thank you for completing this questionnaire.

NAFLD Database

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 **does not** 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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code ____ ____ ____ ____
If report not associated with a visit, fill in "n."

6. Form & revision: a n 1

7. Study: NAFLD Database 1

B. Participant information

8. Date enrolled in NAFLD Database:

____ ____–____ ____ ____–____ ____
day mon year

9. Gender:

Male (1)
Female (2)

10. Age at time of event:

____ ____
years

11. In the past, did the patient ever receive a study drug for a main NASH CRN treatment trial (eg, PIVENS, TONIC) or substudy *(check all that apply)*

a. None: (1)
12.

b. Pioglitazone: (1)

c. Vitamin E: (1)

d. Metformin: (1)

e. Placebo: (1)

f. Other *(specify):* (1)

_____
specify

12. Is the patient currently receiving a study drug or intervention for a NASH CRN pilot or feasibility study or ancillary study:

Yes (1) No (2)
14.

13. Specify the study drug or intervention:

_____

_____

_____

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:

Yes (1) No (2)

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/treatments:

_____

_____

_____

_____

_____

21. Did the event result in significant sequelae:

Yes (1) No (2)

22.

Specify:

_____

_____

_____

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 (1)
Grade 4 - Life threatening or disabling (2)
Grade 5 - Death (*3)

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

25. 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)

_____
specify

g. None of the above (1)

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	(1)
Active	(2)
	29.
Unknown	(3)
	29.

28. Date resolved:

____ ____–____ ____ ____–____ ____
day mon year

29. Additional comments on adverse event:

_____

_____

_____

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.

NAFLD Database

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

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b c 1

7. Study: NAFLD Database 1

B. Check on consent

8. Did the patient/parent consent/assent to blood draw for DNA extraction:

Yes (1) No (* 2) STOP

* *You cannot proceed until you get consent.*

C. Specimen for Genetics Repository

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 the NIDDK Genetics Repository.

9. Was blood collected for the NIDDK Genetics Repository:

Yes (1) → **10.**

No, *(specify):* (2)

_____
specify

→ **14.**

10. Date and time of blood draw

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour minute am pm

11. Number of 10 mL EDTA tubes: ____

12. Form copy of tube labels:

NAFLD DB Form BC
Pt: ccc- 9999, xyz
Gender
Age, yrs.: XX

13. Phlebotomist:

_____
print name

D. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

BD - Food Questionnaire Documentation

Purpose: To document completion of the age appropriate food questionnaire.
When: Visits s2, f048, f096, f144, and f192.
Administered by: Clinical Coordinator.
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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b d 2

7. Study:
NAFLD Database 1

B. Administration of food questionnaire

8. Date food questionnaire booklet was completed:

____ ____–____ ____ ____–____ ____
day mon year

NOTE: The visit s2 food questionnaire may not have been completed more than 8 weeks (56 days) prior to registration for the Database.

9. Which food questionnaire was completed *(check only one)*:

Block 98 (1)
12.
Brief Food Questionnaire (2)

10. How was the Brief Food Questionnaire completed:

Self administered by patient/parent (1)
Interview in English (2)
Interview with translator (3)

11. Who was the respondent *(check all that 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

12. Form copy of label applied to food questionnaire:

NAFLD DB Form BD
Pt: 9999,xyz
Visit: vvvv

Date: _____

C. Administrative information

13. Clinical Coordinator PIN: ____ ____ ____

14. Clinical Coordinator signature:

_____

15. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

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 EXC 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.

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: s 1 ____ ____

6. Form & revision: b g 3

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:

Yes (1) No (2)
10.

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

a. Alcohol related liver disease: (1)
b. Viral hepatitis: (1)
c. Alpha-1 antitrypsin deficiency: (1)
d. Wilson's disease: (1)
e. Glycogen storage disease: (1)
f. Iron overload: (1)
g. Fatty liver disease *(NAFLD, NASH):* (1)
h. Primary liver cancer: (1)
i. Type of liver disease unknown: (1)
j. Other *(specify):* (1)

_____
specify

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

Yes (1) No (2)
12.

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

Yes (1) 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)

14. Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:

Yes (1)
No (2)
Don't know (3)

15. Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood fat:

Yes (1)
No (2)
Don't know (3)

C. NAFLD history

16. Date patient was first diagnosed with fatty liver disease or cryptogenic cirrhosis:

____ ____–____ ____ ____–____ ____
day mon year

17. What prompted the evaluation for NAFLD, NASH, or cryptogenic cirrhosis *(check all that apply)*

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)
e. Other *(specify):* (1)

_____
specify

18. What procedure/tests supported this first diagnosis *(check all that apply)*

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

Yes (1) No (2)

21.

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:

Yes (1) No (2)
21.

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:

Yes (* 1) 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:

Yes (* 1) No (2)

**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)
No or minimal change (6)

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

28. Is the patient age 18 or older:

Yes (1) No (2)
31.

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

____ ____ ____
lbs

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:

Yes (1) No (2)
33.

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

____ ____ ____
lbs

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

Yes (1) No (2)

35.

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:

Yes (1) No (2)

37.

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:

Yes (1) No (2)

43.

38. Have you ever smoked tobacco cigarettes:

Never (1)

43.

In the past but not anymore (2)
Currently smokes cigarettes (3)

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):*

C Yes (1) No (2)

43.

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

____ ____
years

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:

Yes (1) No (2)

49.

44. Has menarche occurred:

Yes (1) No (2)

49.

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

47. Is patient post-menopausal:

Yes (1) No (2)

49.

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: (1)

b. Diabetes type 2: (1)

c. Gestational diabetes *(diabetes of pregnancy):* (1)

d. Hepatitis B: (1)

C

e. Hepatitis C: (1) C

f. Autoimmune hepatitis: (1)

g. Autoimmune cholestatic liver disorder (PBC or PSC): (1) C

h. Wilson's disease: (1) C

i. Alpha-1-antitrypsin (A1AT) deficiency: (1) C

j. Iron overload: (1) C

k. Drug induced liver disease: (1)

l. Gilbert's syndrome: (1)

m. Esophageal or gastric varices on endoscopy: (1)

n. Bleeding from varices: (1)

o. Other gastrointestinal bleeding: (1)

p. Ascites: (1)

q. Edema: (1)

r. Hepatic encephalopathy: (1)

s. Portal hypertension: (1)

t. Hepatorenal syndrome: (1)

u. Hepatopulmonary syndrome: (1)

v. Short bowel syndrome: (1) C

w. Hemophilia *(bleeding disorder):* (1) C

x. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

y. Endocrine disease *(hormonal abnormality):* (1)

z. Hepatocellular carcinoma: (1) C

aa. Other malignancy *(cancer):* (1)

ab. Peripheral neuropathy: (1)

ac. Seizure disorder or epilepsy: (1)

ad. Drug allergies: (1)

ae. Hypothyroidism: (1)

af. Hypertension: (1)

ag. Cerebrovascular disease: (1)

ah. Dysbetalipoproteinemia: (1) C

ai. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

aj. Pancreatitis: (1)

ak. Cholelithiasis: (1)

al. Coronary artery disease: (1)

am. Elevated uric acid such as gout: (1)

an. Kidney disease: (1)

ao. Polycystic ovary syndrome: (1)

ap. Sleep apnea *(not breathing during sleep):* (1)

aq. Dermatologic disorders: (1)

ar. Myopathy: (1)

as. Myositis: (1)

at. Major depression: (1)

au. Schizophrenia: (1)

av. Bipolar disorder: (1)

aw. Obsessive compulsive disorder: (1)

ax. Severe anxiety or personality disorder: (1)

ay. None of the above: (1)

50. Has the patient ever had surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1) C

b. Jejunoileal *(or other intestinal)* bypass: (1) C

c. Biliopancreatic diversion: (1) C

d. Other GI or bariatric surgery *(specify):* (1)

_____

e. None of the above: (1)

51. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

(Yes 1) (No 2)

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

(Yes 1) (No 2)

52. Has the patient received total parenteral nutrition (TPN) in the past 2 years:

(Yes 1) (No 2)

53. Is the patient currently undergoing evaluation for bariatric surgery:

(Yes 1) (No 2)

H. Medication use

54. Has the patient used any antidiabetic medications in the past 6 months *(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): (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: (1)

55. Has the patient taken any alcohol abuse (dependance or withdrawal) medications in the past 6 months *(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)

_____

h. None of the above: (1)

56. Has the patient taken any antihyperlipidemic medications in the past 6 months *(check all that apply):*

a. Atorvastatin (Lipitor): (1)

b. Colestipol hydrochloride (Colestid): (1)

c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)

d. Gemfibrozil (Gen-Fibro, Lopid): (1)

e. Fenofibrate (Tricor): (1)

f. Fluvastatin sodium (Lescol): (1)

g. Lovastatin (Mevacor): (1)

h. Nicotinic acid (Niaspan): (1)

i. Pravastatin sodium (Pravachol): (1)

j. Rosuvastatin (Crestor): (1)

k. Simvastatin (Zocor): (1)

l. Other, *(specify):* (1)

_____

m. None of the above: (1)

57. Has the patient taken any antiobesity medications in the past 6 months *(check all that apply):*

a. Dexfenfluramine hydrochloride (Redux): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

c. Methamphetamine hydrochloride (Desoxyn, Gradumet): (1)

d. Orlistat (Xenical): (1)

e. Phendimetrazine tartrate (Adipost, Bontril): (1)

f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): (1)

g. Sibutramine hydrochloride monohydrate (Meridia): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. 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):*

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. Other, *(specify):* (1)

_____

j. Other, *(specify):* (1)

_____

k. Other, *(specify):* (1)

_____

l. None of the above: (1)

59. Has the patient taken any strong opiates containing acetaminophen medication in the past 6 months *(check all that apply)*

a. Darvocet: (1)

b. Esgic - Plus: (1)

c. Fioricet: (1)

d. Lorcet: (1)

e. Lortab: (1)

f. Norco: (1)

g. Percocet: (1)

h. Talacen: (1)

i. Tylenol #3: (1)

j. Tylenol #4: (1)

k. Tylox: (1)

l. Vicodin: (1)

m. Wygesic: (1)

n. Other, *(specify):* (1)

_____

o. None of the above: (1)

60. Has the patient taken any histamine H2 receptor antagonists/other gastrointestinal medications in the past 6 months *(check all hat 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)

61. Has the patient taken any anticoagulant/antiplatelet medications in the past 6 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)

62. Has the patient taken any systemic corticosteroids in the past 6 months *(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)

63. Has the patient taken any cardiovascular or antihypertensive medications in the past 6 months *(check all that apply):*

a. Amiodarone (Pacerone): (1)
b. Amlodipine besylate (Norvasc): (1)
c. Atenolol (Tenormin): (1)
d. Benazepril (Lotensin): (1)
e. Captopril (Capoten): (1)
f. Clonidine (Catapres): (1)
g. Digoxin (Lanoxin): (1)
h. Diltiazem (Cardizem): (1)
i. Doxazosin (Cardura): (1)
j. Enalapril (Vasotec): (1)
k. Felodipine (Plendil): (1)
l. Furosemide (Lasix): (1)
m. Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)
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): (1)
s. Nifedipine (Adalat, Procardia): (1)
t. Perhexiline maleate: (1)
u. Propranolol (Inderal): (1)
v. Quinapril (Accupril): (1)
w. Terazosin (Hytrin): (1)
x. Timolol maleate (Blocadren): (1)
y. Valsartan (Diovan): (1)
z. Verapamil (Calan): (1)
aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

ac. None of the above: (1)

64. Has the patient taken any estrogen, progestin, hormone replacement therapy, or selective estrogen receptor modulators in the past 6 months *(check all that apply):*

a. Conjugated estrogen (Premarin/Prempro): (1)

b. Diethylstilbestrol and methyltestosterone (Tylosterone): (1)

c. Esterified estrogen (Estratab, Menest): (1)

d. Estradiol (Estrace): (1)

e. Ethinyl estradiol (Estinyl): (1)

f. Fluoxymesterone (Android-F, Halotestin): (1)

g. Levonorgestrel (Norplant): (1)

h. Medroxyprogesterone (Cycrin, Provera): (1)

i. Megestrol (Megace): (1)

j. Methyltestosterone (Android): (1)

k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): (1)

l. Norethindrone (Micronor): (1)

m. Norgestrel (Ovrette): (1)

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)

o. Oxandrolone (Oxandrin): (1)

p. Oxymetholone (Anadrol): (1)

q. Progesterone (Prometrium): (1)

r. Raloxifene (Evista): (1)

s. Tamoxifen (Nolvadex): (1)

t. Other, *(specify):* (1)

_____

u. Other, *(specify):* (1)

_____

v. None of the above: (1)

65. Has the patient taken any allergy or asthma medications in the past 6 months *(check all that apply):*

a. Albuterol: (1)

b. Beclomethasone dipropionate (Beclovent, Vanceril): (1)

c. Budesonide (Pulmicort, Rhinocort): (1)

d. Fluticasone propionate (Flonase, Flovent): (1)

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

g. Triamcinolone acetonide (Azmacort, Nasacort): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

66. Has the patient taken a multivitamin regularly in the past 6 months:

Yes (1) No (2)

67. Has the patient taken vitamins other than multivitamins in the past 6 months:

Yes (1) No (2)

69.

68. Which vitamins has the patient taken *(check all that apply):*

a. Vitamin B (any type): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Vitamin E: (1)

e. Other, *(specify):* (1)

_____

69. Has the patient taken any supplements in the past 6 months *(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): (1)
i. Cod liver oil: (1)
j. Coenzyme Q: (1)
k. Dichloroacetate: (1)
l. 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)

_____

ad. Other, *(specify):* (1)

_____

ae. None of the above: (1)

70. Has patient taken any of the following medications or other supplements/medications in the past 6 months *(record all other supplements/medications):*

a. Demeclocycline (Declomycin): (1)
b. Divalproex (Depakote): (1)
c. Doxycycline (Monodox): (1)
d. Isotretinoin (Accutane): (1)
e. Levothyroxine (Levoxyl, Synthroid): (1)
f. Liothyronine (Cytomel): (1)
g. Methotrexate (Rheumatrex): (1)
h. Minocycline (Dynacin, Minocin): (1)
i. Oxytetracycline (Terramycin): (1)
j. Penicillamine (Cuprimine, Depen): (1)
k. Tetracycline (Achromycin): (1)
l. Trientine hydrochloride (Syprine): (1)
m. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)
n. Valproate sodium (Depacon): (1)
o. Valproic acid (Depakene): (1)
p. Other, *(specify):* (1)

_____

q. Other, *(specify):* (1)

_____

r. Other, *(specify):* (1)

_____

s. Other, *(specify):* (1)

_____

t. Other, *(specify):* (1)

_____

u. None of the above: (1)

I. Administrative information

71. Study Physician PIN: ____ ____ ____

72. Study Physician signature:

_____

73. Clinical Coordinator PIN: ____ ____ ____

74. Clinical Coordinator signature:

_____

75. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon 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 colleced will not be able to be determined.

A. Center, patient and visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b p 1

7. Study: NAFLD Database 1

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)

23. ____

No, other reason *(specify):* (3)

23. ____

_____
specify other reason

9. Date and time of blood draw

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour minute am pm

10. Number of CTAD (blue-top) tubes: ____

11. Attach duplicate CTAD tube label:

NAFLD DB Form, BP Pl.
Pt: 9999, xyz
Visit vvvv
Date: _____

12. Number of SST serum separator tubes (red-top) tubes: ____

13. Attach duplicate SST serum separator tube labels:

NAFLD DB Serum 1 Pt: 9999, xyz Visit: vvvv BP Date: _____	NAFLD DB Serum 2 Pt: 9999, xyz Visit: vvvv BP Date: _____
NAFLD DB Serum 3 Pt: 9999, xyz Visit: vvvv BP Date: _____	NAFLD DB 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 six 2.0 mL pre-labeled cryovials and pour 0.5 mL of serum into each of forty 2.0 mL pre-labeled cryovials.

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 for plasma: ____

17. Number of aliquots for serum: ____ ____

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. Date and time cryovials frozen in -70°C or -20°C

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour minute am pm

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

NAFLD Database

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 open).
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 form.

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: c g 1

7. Study: NAFLD Database 1

B. Consent for collection, storage, and use of blood samples for current and future genetic research

8. Does the patient/parent consent to genetic research on NAFLD or cryptogenic cirrhosis that is currently planned by the study investigators:

(Yes 1) (No 2)

9. Does the patient/parent consent to future genetic research on NAFLD or cryptogenic cirrhosis by this study or other study investigators:

(Yes 1) (No 2)

10. Does the patient/parent consent to future genetic research not related to NAFLD or cryptogenic cirrhosis by this study or other study investigators:

(Yes 1) (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/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 8 through 10; a response of "No" to this question (item 12) means that blood should NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):*

(Yes 1) (No 2)

C. Administrative information

13. Study Physician PIN: ____ ____ ____

14. Study Physician signature:

_____

15. Clinical Coordinator PIN: ____ ____ ____

16. Clinical Coordinator signature:

_____

17. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon 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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit *(date form in initiated; effective date for suspension of visit completion):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: c o 1

7. Study: NAFLD Database 1

B. New study information

8. Study that patient has been or will be randomized in *(check only one):*

PIVENS (1)
TONIC (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

C. Administrative information

10. Clinical Coordinator PIN: ____ ____ ____

11. Clinical Coordinator signature:

_____

12. 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

c r 1 6. Form and revision

__ 7. Study: **1**=Database; **2**=PIVENS; **3**=TONIC

__ __ / __ __ __ / __ __ 8. Date of biopsy

B. Slide sequence number

9. 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

16. 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. Microvesicular steatosis, contiguous patches: **0**=Absent; **1**=Present

17. 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

_____ . . . b. Microgranulomas seen: **0**=No; **1**=Yes

_____ . . . c. Large lipogranulomas seen: **0**=No; **1**=Yes

_____ . . . d. Amount of portal, chronic inflammation: **0**=None; **1**=Mild; **2**=More than mild

18. Liver cell injury

_____ . . . a. Ballooning: **0**=None; **1**=Few; **2**=Many

_____ . . . b. Acidophil bodies: **0**=Rare/absent; **1**=Many

_____ . . . c. Pigmented macrophages (*Kupffer cells*): **0**=Rare/absent; **1**=Many

_____ . . . d. Megamitochondria: **0**=Rare/absent; **1**=Many

_____ 19. Mallory's hyaline: **0**=Rare/absent; **1**=Many

_____ 20. Glycogen nuclei: **0**=Rare/absent; **1**=Many

Masson's trichrome stain

_____ 21. Fibrosis stage: **0**=None; **1a**=Mild, zone 3 perisinusoidal (*requires trichrome*);
1b=Moderate, zone 3, perisinusoidal (*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 grade: **0**=Absent or barely discernible, 40x ➜ **GOTO item 22c**;
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 23**; **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

_____ 23. Is this steatohepatitis? **0**=No; **1a**=Suspicious/borderline/indeterminate: Zone 3 pattern;
1b=Suspicious/borderline/indeterminate: Zone 1, periportal pattern; **2**=Yes, definite

_____ 24. Is cirrhosis present? **0**=No ➜ **GOTO item 27**; **1**=Yes

_____ 25. Is this cryptogenic cirrhosis: **0**=No ➜ **GOTO item 27**; **1**=Yes

26. Features suggestive of steatohepatitis etiology for cryptogenic cirrhosis:

_____ . . . a. Mallory's hyaline (*rule out cholate stasis*): **0**=Absent; **1**=Present

_____ . . . b. Perisinusoidal fibrosis away from septa: **0**=Absent; **1**=Present

_____ . . . c. Hepatocyte ballooning: **0**=Absent; **1**=Present

_____ . . . d. Megamitochondria: **0**=Absent; **1**=Present

_____ . . . e. Other notable findings: **0**=Absent; **1**=Present; Specify: _____

27. Other comments: _____

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: d r 1

7. Study: NAFLD Database 1

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Health care provider or NASH CRN staff: (1)
d. Newspaper: (1)
e. Funeral parlor/home: (1)
f. Medical record: (1)
g. Medical examiner: (1)
h. Coroner: (1)
i. Other *(specify):* (1)

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

11. Cause of death
(Study Physician: use whatever knowledge you have and your best medical judgment to best characterize the cause of death; check only one):

Heart disease (1)
Stroke (2)
Liver disease (3)
Malignancy (4)
Other *(specify):* (5)

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

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 Elig 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 STOP or Elig 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: s 2 ____ ____

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	(7)

Elig

* *Patient is ineligible if female*

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:

Yes (1) No (2)
Elig

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:

Yes (1) No (2)
Elig

b. Short bowel syndrome:

Yes (1) No (2)
Elig

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)*:

Yes (1) No (2)
Elig

d. History of biliopancreatic diversion:

Yes (1) No (2)
Elig

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):* ____ 1-3

b. Serum total bilirubin subscore *(from Form LR: < 2.0 mg/dL=1, 2.0-3.0=2, > 3.0=3):* ____ 1-3

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

f. Child-Pugh Turcotte score *(sum items 11a + 11b + 11c + 11d + 11e):* ____ ____ 5-15

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

Yes (1) → Elig; No (2)

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):*

Yes (1) → Elig; No (2)

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

Yes (1) → Elig; No (2)

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

Yes (1) → Elig; No (2)

d. Wilson's disease:

Yes (1) → Elig; No (2)

e. Known glycogen storage disease:

Yes (1) → Elig; No (2)

f. Known dysbetalipoproteinemia:

Yes (1) → Elig; No (2)

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

Yes (1) → Elig; No (2)

h. Congenital hepatic fibrosis, polycystic liver disease:

Yes (1) → Elig; No (2)

i. Other metabolic/congenital liver disease:

Yes (1) → Elig; No (2)

j. HIV infection or other systemic infectious disease:

( ) Yes (1) ( ) No (2) → Elig

k. Disseminated or advanced extrahepatic malignancy:

( ) Yes (1) ( ) No (2) → Elig

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

( ) Yes (1) ( ) No (2) → Elig

13. Do any of the patient's assessments show evidence of these histologic exclusions

a. Hepatic iron index > 1.9:

( ) Yes (1) ( ) No (2) → Elig

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

( ) Yes (1) ( ) No (2) → Elig

c. Chronic cholestasis:

( ) Yes (1) ( ) No (2) → Elig

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

( ) Yes (1) ( ) No (2) → Elig

e. Iron overload greater than 3+:

( ) Yes (1) ( ) No (2) → Elig

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

( ) Yes (1) ( ) No (2) → Elig

g. Multiple epithelioid granulomas:

( ) Yes (1) ( ) No (2) → Elig

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:

( ) Yes (1) ( ) No (2) → Elig

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:

Yes ( ) (1)
No ( ) (2)
No biopsy available ( ) (3)

16a.

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

____ ____–____ ____ ____–____ ____
day mon year

16. Cryptogenic cirrhosis on biopsy

a. Did at least one biopsy show cryptogenic cirrhosis:

Yes ( ) (1)
No ( ) (2)
No biopsy available ( ) (3)

17.

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 (1) No (2)

19.

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: (1)

19. Does the patient have an imaging study obtained in the past year compatible with cirrhosis *(small liver, nodularity, heterogeneous echo pattern):*

Yes (1) No (2)

22.

20. Imaging studies suggestive of cirrhosis *(check all that apply)*

a. Upper abdominal ultrasound: (1)

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):* (1)

b. Albumin less than 3.5 g/dL: (1)

c. INR greater than 1.3: (1)

d. Platelet count less than 140,000 cells/uL: (1)

e. Esophageal or gastric varices on endoscopy: (1)

f. Ascites on physical exam or imaging study: (1)

g. None of the above: (1)

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)* (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)* (5)

None of the above (6)

EHg

F. Eligibility check

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

Yes (1) No (2)

26.

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 (1)
26.

No (2)

Task not run because patient is known to be ineligible (* 3)
26.

**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):*

Yes (* 1) No (2)

27. Elig

**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 covered in items 8-14, 22, or 25: (1)

b. Tests are outside time window and clinic chose not to repeat tests: (1)

c. Other reason not covered on this form *(specify):* (1)

_____

H. Administrative information

27. Study Physician PIN: ____ ____ ____

28. Study Physician signature:

_____

29. Clinical Coordinator PIN: ____ ____ ____

30. Clinical Coordinator signature:

_____

31. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: f i 1

7. Study: NAFLD Database 1

B. Study identifiers of children of the index patient recorded in Section A

8. How many children of the index patient identified in item 2 are enrolled in NAFLD Database, PIVENS, and TONIC
(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):

____
0-5

If zero (0), then skip to item 14.

9. First child

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

Skip to item 14 if there are no more children enrolled in NAFLD, PIVENS, or TONIC.

10. Second child

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

Skip to item 14 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

11. Third child

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

Skip to item 14 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

12. Fourth child

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

Skip to item 14 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

13. Fifth child

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

Call the DCC for instructions if there are more children enrolled in NAFLD Database, PIVENS, or TONIC.

C. Study identifiers of sibling(s) of the index patient recorded in Section A

14. How many siblings of the index patient identified in item 2 are enrolled in NAFLD Database, PIVENS, and TONIC *(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):* ____ 0-5

If zero (0), then skip to item 20.

15. First sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

16. Second sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

17. Third sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

18. Fourth sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 20 if there are no more children enrolled in NAFLD Database, PIVENS, or TONIC.

19. Fifth sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Call the DCC for instructions if there are more children enrolled in NAFLD Database, PIVENS, or TONIC.

D. Study identifiers of the parents of the index patient identified in section A *(call the DCC if more than 1 mother and/or 1 father are enrolled in NAFLD Database and PIVENS)*

20. Mother of index patient

a. Is the mother of the index patient enrolled in NAFLD Database or PIVENS):

Yes (1) No (2)

21.

b. Patient ID: ____ ____ ____ ____

c. Patient code: ____ ____ ____

d. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

21. Father of index patient

a. Is the father of the index patient enrolled in NAFLD Database or PIVENS):

Yes (1) No (2)

22.

b. Patient ID: ____ ____ ____ ____

c. Patient code: ____ ____ ____

d. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

E. Administrative information

22. Clinical coordinator PIN: ____ ____ ____

23. Clinical coordinator signature:

_____

24. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of reading:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: h e 1

7. Study: NAFLD Database 1

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)

b. Masson's trichrome: (1)

C. NAFLD evaluation (use H & E and Masson's trichrome slides only)

10. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5%	(0)
5-33%	(1)
34-66%	(2)
> 66%	(3)

b. Location:

Zone 3	(0)
Zone 1	(1)
Azonal	(2)
Panacinar	(3)

11. Fibrosis stage *(Masson's trichrome stain)*

0: None	(0)
1a: Zone 3, perisinusoidal (requires trichome)	(1)
1b: Zone 3, perisinusoidal (easily seen on H&E)	(2)
1c: Portal/periportal only	(3)
2: Zone 3 and periportal, any combination	(4)
3: Bridging	(5)
4: Cirrhosis	(6)

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)
> 4 / 20x mag (3)

b. Amount of portal, chronic inflammation:

None to minimal (0)
Greater than minimal (1)

13. Hepatocellular ballooning:

None (0)
Few (1)
Many (2)

14. Is steatohepatitis present:

No (1)
Suspicious/borderline/indeterminate (2)
Yes, definite (3)

D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:

Yes (1) No (2)

16. Is there evidence of Wilson's disease:

Yes (* 1) No (2)

→ C

** Caution: Wilson's disease is exclusionary*

17. Features of chronic cholestatic liver disease *(check all that apply)*

a. Bile duct loss/infiltration/sclerosis: (1)
b. Florid duct lesions: (1)
c. Cholate stasis: (1)
d. Copper deposition: (1)
e. Other *(specify):* (1)

_____

f. None: (1)

18. Features of other forms of chronic liver disease *(check all that apply)*

a. Vascular lesions of ALD/B-C/OVD: (1)
b. Inflammation suggestive of AIH, HCV: (1)
c. Pigment suggestive of HH: (1)
d. Globules suggestive of A1AT: (1)
e. Hepatocellular changes suggestive of HBV: (1)
f. Granulomas suggestive of sarcoid, PBC, infection: (1)
g. Other *(specify):* (1)

_____

h. None: (1)

E. Evaluation of cryptogenic cirrhosis

19. Is cirrhosis present:

Yes (1) No (2)

→ **22.**

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):

Yes (1) No (2)

→ **22.**

F. Other features

21. Other features *(check all that apply)*

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)

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

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of reading:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: h f 1

7. Study: NAFLD Database 1

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)

b. Masson's trichrome: (1)

C. NAFLD evaluation (use H & E and Masson's trichrome slides only)

10. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5% (0)
5-33% (1)
34-66% (2)
> 66% (3)

b. Location:

Zone 3 (0)
Zone 1 (1)
Azonal (2)
Panacinar (3)

11. Fibrosis stage *(Masson's trichrome stain)*

0: None (0)
1a: Zone 3, perisinusoidal (requires trichome) (1)
1b: Zone 3, perisinusoidal (easily seen on H&E) (2)
1c: Portal/periportal only (3)
2: Zone 3 and periportal, any combination (4)
3: Bridging (5)
4: Cirrhosis (6)

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)
> 4 / 20x mag	(3)

b. Amount of portal, chronic inflammation:

None to minimal	(0)
Greater than minimal	(1)

13. Hepatocellular ballooning:

None	(0)
Few	(1)
Many	(2)

14. Is steatohepatitis present:

No	(1)
Suspicious/borderline/indeterminate	(2)
Yes, definite	(3)

D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:

Yes (1) No (2)

16. Is there evidence of Wilson's disease:

Yes (* 1) No (2)

→ C

** Caution: Wilson's disease is exclusionary*

17. Features of chronic cholestatic liver disease *(check all that apply)*

a. Bile duct loss/infiltration/sclerosis:	(1)
b. Florid duct lesions:	(1)
c. Cholate stasis:	(1)
d. Copper deposition:	(1)
e. Other *(specify):*	(1)

_____

f. None:	(1)

18. Features of other forms of chronic liver disease *(check all that apply)*

a. Vascular lesions of ALD/B-C/OVD:	(1)
b. Inflammation suggestive of AIH, HCV:	(1)
c. Pigment suggestive of HH:	(1)
d. Globules suggestive of A1AT:	(1)
e. Hepatocellular changes suggestive of HBV:	(1)
f. Granulomas suggestive of sarcoid, PBC, infection:	(1)
g. Other *(specify):*	(1)

_____

h. None:	(1)

E. Evaluation of cryptogenic cirrhosis

19. Is cirrhosis present:

Yes (1) No (2)

→ **22.**

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):

Yes (1) No (2)

→ **22.**

F. Other features

21. Other features *(check all that apply)*

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)

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

NAFLD Database

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

Purpose: Record results of histologic evaluation of slides from **next 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of reading:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: h g 1

7. Study: NAFLD Database 1

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)

b. Masson's trichrome: (1)

C. NAFLD evaluation (use H & E and Masson's trichrome slides only)

10. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5%	(0)
5-33%	(1)
34-66%	(2)
> 66%	(3)

b. Location:

Zone 3	(0)
Zone 1	(1)
Azonal	(2)
Panacinar	(3)

11. Fibrosis stage *(Masson's trichrome stain)*

0: None	(0)
1a: Zone 3, perisinusoidal (requires trichome)	(1)
1b: Zone 3, perisinusoidal (easily seen on H&E)	(2)
1c: Portal/periportal only	(3)
2: Zone 3 and periportal, any combination	(4)
3: Bridging	(5)
4: Cirrhosis	(6)

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)
> 4 / 20x mag (3)

b. Amount of portal, chronic inflammation:

None to minimal (0)
Greater than minimal (1)

13. Hepatocellular ballooning:

None (0)
Few (1)
Many (2)

14. Is steatohepatitis present:

No (1)
Suspicious/borderline/indeterminate (2)
Yes, definite (3)

D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:

Yes (1) No (2)

16. Is there evidence of Wilson's disease:

Yes (* 1) No (2)

C

** Caution: Wilson's disease is exclusionary*

17. Features of chronic cholestatic liver disease *(check all that apply)*

a. Bile duct loss/infiltration/sclerosis: (1)
b. Florid duct lesions: (1)
c. Cholate stasis: (1)
d. Copper deposition: (1)
e. Other *(specify):* (1)

_____

f. None: (1)

18. Features of other forms of chronic liver disease *(check all that apply)*

a. Vascular lesions of ALD/B-C/OVD: (1)
b. Inflammation suggestive of AIH, HCV: (1)
c. Pigment suggestive of HH: (1)
d. Globules suggestive of A1AT: (1)
e. Hepatocellular changes suggestive of HBV: (1)
f. Granulomas suggestive of sarcoid, PBC, infection: (1)
g. Other *(specify):* (1)

_____

h. None: (1)

E. Evaluation of cryptogenic cirrhosis

19. Is cirrhosis present:

Yes (1) No (2)

22.

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):

Yes (1) No (2)

22.

F. Other features

21. Other features *(check all that apply)*

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)

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

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: h i 1

7. Study: NAFLD Database 1

B. Interval identification

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

____ ____–____ ____ ____–____ ____
day mon year

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:

Yes (*1) No (2)

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

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

Yes (*1) No (2)

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

D. Alcohol consumption (AUDIT-C) since the last visit

12. Is the patient age 8 or older:

Yes (1) No (2)

19.

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

Never	(0)
	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	(4)

14. 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)

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)

E. Tobacco cigarette smoking

16. Since the last visit, have you smoked tobacco cigarettes regularly *("No" means smoked less than 1 day per week on average):*

(Yes 1) (No 2)

19.

17. On average, how many days per week have you smoked cigarettes:

____ # days

18. On the days that you smoked, about how many cigarettes did you smoke per day:

____ ____ ____ # cigarettes per day

F. Medical history

19. 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)*

a. Diabetes type 1: (1)

b. Diabetes type 2: (1)

c. Gestational diabetes *(diabetes of pregnancy):* (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)

l. Gilbert's syndrome: (1)

m. Esophageal or gastric varices on endoscopy: (1)

n. Bleeding from varices: (1)

o. Other gastrointestinal bleeding: (1)

p. Ascites: (1)

q. Edema: (1)

r. Hepatic encephalopathy: (1)

s. Portal hypertension: (1)

t. Hepatorenal syndrome: (1)

u. Hepatopulmonary syndrome: (1)

v. Short bowel syndrome: (1)

w. Hemophilia *(bleeding disorder):* (1)

x. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

y. Endocrine disease *(hormonal abnormality):* (1)

z. Hepatocellular carcinoma: (1)

aa. Other malignancy *(cancer):* (1)

ab. Peripheral neuropathy: (1)

ac. Seizure disorder or epilepsy: (1)

ad. Drug allergies: (1)

ae. Hypothyroidism: (1)

af. Hypertension: (1)

ag. Cerebrovascular disease: (1)

ah. Dysbetalipoproteinemia: (1)

ai. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

aj. Pancreatitis: (1)

ak. Cholelithiasis: (1)

al. Coronary artery disease: (1)

am. Elevated uric acid such as gout: (1)

an. Kidney disease: (1)

ao. Polycystic ovary syndrome: (1)

ap. Sleep apnea *(not breathing during sleep):* (1)

aq. Dermatologic disorders: (1)

ar. Myopathy: (1)

as. Myositis: (1)

at. Major depression: (1)

au. Schizophrenia: (1)

av. Bipolar disorder: (1)

aw. Obsessive compulsive disorder: (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)*

a. Stapling or banding of the stomach: (1)

b. Jejunoileal *(or other intestinal)* bypass: (1)

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 (1) No (2)

22. Since the last visit, has the patient received total parenteral nutrition (TPN):

Yes (1) No (2)

23. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) No (2)

24. Since the last visit, has the patient been hospitalized:

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 (2)

26.

If Yes, specify:

_____

specify

G. Medication use

26. 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): (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: (1)

27. Since the last visit, has the patient taken any alcohol abuse (dependance or withdrawal) medications *(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)

_____

h. None of the above: (1)

28. Since the last visit, has the patient taken any antihyperlipidemic medications *(check all that apply):*

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

_____

m. None of the above: (1)

29. Since the last visit, has the patient taken any antiobesity medications *(check all that apply):*

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

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

30. Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications *(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. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. Other, *(specify):* (1)

_____

k. None of the above: (1)

31. Has the patient taken any strong opiates containing acetaminophen medication in the past 6 months *(check all that apply)*

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

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)

34. 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)

35. Since the last visit, has the patient taken any cardiovascular/antihypertensive medications *(check all that apply):*

a. Amiodarone (Pacerone): (1)
b. Amlodipine besylate (Norvasc): (1)
c. Atenolol (Tenormin): (1)
d. Benazepril (Lotensin): (1)
e. Captopril (Capoten): (1)
f. Clonidine (Catapres): (1)
g. Digoxin (Lanoxin): (1)
h. Diltiazem (Cardizem): (1)
i. Doxazosin (Cardura): (1)
j. Enalapril (Vasotec): (1)
k. Felodipine (Plendil): (1)
l. Furosemide (Lasix): (1)
m. Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)
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): (1)
s. Nifedipine (Adalat, Procardia): (1)
t. Perhexiline maleate: (1)
u. Propranolol (Inderal): (1)
v. Quinapril (Accupril): (1)
w. Terazosin (Hytrin): (1)
x. Timolol maleate (Blocadren): (1)
y. Valsartan (Diovan): (1)
z. Verapamil (Calan): (1)
aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

ac. None of the above: (1)

36. Since the last visit, has the patient taken any estrogen, progestin, hormone replacement therapy, or selective estrogen receptor modulators *(check all that apply):*

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

_____

u. Other, *(specify):* (1)

_____

v. None of the above: (1)

37. 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): (1)

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

g. Triamcinolone acetonide (Azmacort, Nasacort): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

38. Since the last visit, has the patient taken a multivitamin regularly:

Yes (1) No (2)

39. Since the last visit, has the patient taken vitamins other than multivitamins:

Yes (1) No (2)

41.

40. Which vitamins has the patient taken *(check all that apply)*

a. Vitamin B (any type): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Vitamin E: (1)

e. Other, *(specify):* (1)

_____

41. Since the last visit, has the patient taken any supplements *(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): (1)

i. Cod liver oil: (1)

j. Coenzyme Q: (1)

k. Dichloroacetate: (1)

l. 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)

_____

ad. Other, *(specify):* (1)

_____

ae. None of the above: (1)

42. Since the last visit, has patient taken any of the following medications or other supplements/medications *(record all other supplements/medications):*

a. Demeclocycline (Declomycin): (1)
b. Divalproex (Depakote): (1)
c. Doxycycline (Monodox): (1)
d. Isotretinoin (Accutane): (1)
e. Levothyroxine (Levoxyl, Synthroid): (1)
f. Liothyronine (Cytomel): (1)
g. Methotrexate (Rheumatrex): (1)
h. Minocycline (Dynacin, Minocin): (1)
i. Oxytetracycline (Terramycin): (1)
j. Penicillamine (Cuprimine, Depen): (1)
k. Tetracycline (Achromycin): (1)
l. Trientine hydrochloride (Syprine): (1)
m. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)
n. Valproate sodium (Depacon): (1)
o. Valproic acid (Depakene): (1)
p. Other, *(specify):* (1)

_____

q. Other, *(specify):* (1)

_____

r. Other, *(specify):* (1)

_____

s. Other, *(specify):* (1)

_____

t. Other, *(specify):* (1)

_____

u. None of the above: (1)

H. Summary judgments about specific liver conditions *(these judgments are to be made after all of the visit data are collected)*

43. 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 (3)

I. 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

NAFLD Database

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: i e 1

7. Study: NAFLD Database 1

B. Visit interval identification

8. Most recently completed visit (screening or followup)

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____ ____

C. Patient information

9. Date enrolled in NAFLD Database *(enter n if patient is not yet enrolled):*

____ ____–____ ____ ____–____ ____
day mon year

10. Gender:

Male (1)
Female (2)

11. Age at time of event: ____ ____ years

D. Event description

12. Date event started:

____ ____–____ ____ ____–____ ____
day mon year

13. Is the event associated with prior PIVENS study drug use:

Yes (1) No (2)

16.

14. 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)

15. 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)

16. Is the event associated with prior TONIC study drug use:

(Yes 1) (No 2)

19.

17. 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)

18. 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)

19. Nature of event *(check all that apply)*

a. General anesthesia:	(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. Other *(specify):*	(1)

_____

_____

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)

_____

_____

22. Severity grade *(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 Serious Adverse Event Report (AN) to report serious and unexpected adverse events or call the DCC if unsure what to do:*

Not applicable	(0)
Grade 1 - Mild	(1)
Grade 2 - Moderate	(2)
Grade 3 - Severe	(3)
Grade 4 - Life threatening or disabling	(4)
Grade 5 - Death	(*5)

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

23. Date event resolved *(enter n if event is not yet resolved):*

____ ____–____ ____ ____–____ ____
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:

____ ____–____ ____ ____–____ ____
day mon year

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.

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:
____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: i r 1

7. Study: NAFLD Database 1

B. Upper abdominal ultrasound

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

(Yes 1) (No 2) → **11.**

9. Date of most recent upper abdominal ultrasound:
____ ____–____ ____ ____–____ ____
day mon year

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

a. Fatty infiltration: (1)
b. Cirrhosis: (1)
c. Hepatomegaly: (1)
d. Hepatic mass: (1)
e. Intrahepatic biliary dilatation: (1)
f. Extrahepatic biliary dilatation: (1)
g. Gallstones/cholelithiasis: (1)
h. Gall bladder polyps: (1)
i. Cholecystectomy: (1)
j. Splenomegaly: (1)
k. Ascites: (1)
l. Other features of portal hypertension *(specify):* (1)

_____

_____

m. Other abnormality *(specify):* (1)

_____

_____

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)*:

(Yes 1) (No 2)

14.

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

_____

_____

o. Other abnormality *(specify):* (1)

_____

_____

p. None of the above: (1)

D. Upper abdominal MRI

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

(Yes 1) (No 2)

17.

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)*

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. Splenomegaly: (1)
j. Ascites: (1)
k. Other features of portal hypertension *(specify):* (1)

_____

_____

l. Other abnormality *(specify):* (1)

_____

_____

m. None of the above: (1)

E. Administrative information

17. Study Physician PIN: ____ ____ ____

18. Study Physician signature:

_____

19. Clinical Coordinator PIN: ____ ____ ____

20. Clinical Coordinator signature:

_____

21. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

LD – Lifetime Drinking History (Skinner)

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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **l d 1**

7. Study: NAFLD Database 1

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):

Yes (1) No (2)

81. ◄

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)*	(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)*:

		Positive	Negative	Neutral
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)

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 ____ ____ % ____

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 ____ ____ ____ %

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":

Yes (1) No (2)

81. ◄

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:

Yes (1) No (2)

30. ◄

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)*:

	Positive	Negative	Neutral
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)

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 ____ ____ ____ %

With others ____ ____ ____ %

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 be "000")*:

Morning ____ ____ ____ %

Afternoon ____ ____ ____ %

Evening ____ ____ ____ %

E. Next 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 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 (1) No (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:

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")*:

Beer ____ ____ ____ %

Liquor ____ ____ ____ %

Wine ____ ____ ____ %

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)

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

Yes (1) No (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)*:

	Positive	Negative	Neutral
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":

Yes (1) No (2)

→ **81.**

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

a. Years: ____ ____ yrs

b. Months: ____ ____ mos

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:

____ ____ # drinks

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

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 (1) No (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)*:

	Positive	Negative	Neutral
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"*:

Yes (1) No (2)

81. ◄

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

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

____ ____
drinks

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

____ ____
days

61. 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.*)

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 ____ ____ ____
%

Liquor ____ ____ ____
%

Wine ____ ____ ____
%

63. 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)

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

Yes (1) No (2)

66. ◄

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 effect)*:

	Positive	Negative	Neutral
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)

66. 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 ____ ____ ____
%

67. 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 ____ ____ ____
%

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 (1) No (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.*)

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 ____ ____ % ____

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)

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

Yes (1) No (2)

78. ↵

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)*:

	Positive	Negative	Neutral
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)

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 all 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 ____ ____ ____ %

Evening ____ ____ ____ %

I. Number of phases

80. Are there any additional subsequent phases:

Yes (*1) No (2)

***** *If yes, complete a second LD form.*
Skip sections B and C on second form.

J. Administrative information

81. Clinical Coordinator PIN: ____ ____ ____

82. Clinical Coordinator signature:

_____

83. Date form reviewed:

____ ____-____ ____ ____-____ ____
day mon year

NAFLD Database 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), interviewer 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.

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: **l p 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient/parent (1) → **10.**
Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that 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

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
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 affects you *(choose only one)*:

Circle one

I feel normal and am not tired **(If this is how you feel, please circle "1" and go 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 2
At least part of several days a week 3
At least part of one day a week 4
Not as much as above 5

15. Are you tired *(choose only one)*:

When you wake up in the morning 1
Or does it come on with the day 2
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
No 2

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.

NAFLD Database

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. 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: **l q 1**

7. Study: NAFLD Database 1

B. Administrative information
(To be completed by Clinical Coordinator after survey is completed.)

8. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

9. 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 (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
l. 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

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	3
I have fatigue and it keeps me from doing what I want to do	4
I have fatigue that prevents me from working	5
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	2
At least part of several days a week	3
At least part of one day a week	4
Less frequently	5

13. Is your fatigue typically present *(choose only one)*:

When you wake up in the morning	1
Or does it come on with the day	2
Or does it have no time pattern	3

14. Is your fatigue typically worse the day after a period of extra activity or exercise:

Yes	1
No	2

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):

Circle one

Yes 1
No 2

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

Very good 1
Good 2
Fair 3
Poor 4
Awful 5

17. Today's date:

_____

Thank you for completing this questionnaire.

NAFLD Database

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/μL, 1000 cells/μL, 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit *(date form was initiated):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: 1 r 3

7. Study: NAFLD Database 1

B. Hematology

8. Date of blood draw for complete blood count:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database visit time window guide).

9. Hemoglobin: ____ ____ ____ • ____ g/dL

10. Hematocrit: ____ ____ ____ • ____ %

11. White blood cell count (WBC):

____ ____ ____ ____ • ____
10^3 cells/μL or 10^9 cells/L

12. Platelet count:

____,____ ____ ____,____ ____ ____
cells/ μL

C. Chemistries and HbA1c

13. Date of blood draw for chemistries:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database visit time window guide).

14. Sodium:* ____ ____ ____ mEq/L

15. Potassium:* ____ ____ ____ • ____ mEq/L

16. Chloride:* ____ ____ ____ mEq/L

17. Bicarbonate:* ____ ____ ____ • ____ mEq/L

18. Calcium:* ____ ____ ____ • ____ mg/dL

19. Phosphate:* ____ ____ ____ • ____ mg/dL

20. Blood urea nitrogen (BUN): ____ ____ mg/dL

21. Creatinine: ____ ____ ____ • ____ mg/dL

22. Uric acid: ____ ____ ____ • ____ mg/dL

** Optional: If not done, enter "m".*

23. Date of blood draw for HbA1c:

____ ____–____ ____ ____–____ ____
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 Database visit time window guide).

24. HbA1c: ____ ____ • ____ %

D. Liver panel and alpha feto protein

25. Date of blood draw for liver panel:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database visit time window guide).

26. Bilirubin (total): ____ ____ • ____ mg/dL

27. Bilirubin (direct): ____ ____ • ____ mg/dL

28. Aspartate aminotransferase (AST)

____ ____ ____ ____ U/L

a. Upper limit of normal: ____ ____ ____ ____ U/L

b. Lower limit of normal: ____ ____ ____ U/L

29. Alanine aminotransferase (ALT)

____ ____ ____ ____ U/L

a. Upper limit of normal: ____ ____ ____ ____ U/L

b. Lower limit of normal: ____ ____ ____ U/L

30. Alkaline phosphatase ____ ____ ____ ____ U/L

a. Upper limit of normal: ____ ____ ____ ____ U/L

b. Lower limit of normal: ____ ____ ____ U/L

31. Gamma glutamyl transferase (GGT):

____ ____ ____ U/L

32. Total protein: ____ ____ • ____ g/dL

33. Albumin: ____ • ____ g/dL

34. Prothrombin time (PT): ____ ____ • ____ sec

35. International normalized ratio (INR):

____ • ____

36. Date of blood draw for alpha feto protein:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database visit time window guide). Record "m" if test not done.

37. Alpha feto protein:

____ ____ ____ ____ • ____ ____
ng/mL

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.

38. Date of blood draw for fasting lipid profile:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database visit time window guide).

a. Triglycerides: ____ ____ ____ ____ mg/dL

b. Total cholesterol: ____ ____ ____ mg/dL

c. HDL cholesterol: ____ ____ ____ mg/dL

d. LDL cholesterol: ____ ____ ____ mg/dL

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.

39. Date of blood draw for fasting glucose and insulin levels:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database visit time window guide).

a. Serum glucose: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ μU/mL

G. Administrative information

40. Study Physician PIN: ____ ____ ____

41. Study Physician signature:

_____

42. Clinical Coordinator PIN: ____ ____ ____

43. Clinical Coordinator signature:

_____

44. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

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 (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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: 1 s 1

7. Study: NAFLD Database 1

B. Screening etiologic tests

8. 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. *Record as ''m'' if test is not done.*

a. Hepatitis B surface antigen (HBsAg):
Positive (1) ⊘ ____
Negative (2)

b. Hepatitis B core total antibody (anti-HBc) *(if total anti-HBc is not available, record results from IgG test)*:*
Positive (1)
Negative (2)

c. Hepatitis B surface antibody (anti-HBs)*:
Positive (1)
Negative (2)

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 (1) ⊘ ____
Negative (2)

e. Hepatitis C virus RNA:
Positive (1) ⊘ ____
Negative (2)
Not available (3)

f. Hepatitis A virus antibody (anti-HAV, total):
Positive (1)
Negative (2)
Not available (3)

C. Iron

9. 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

b. Total iron binding capacity: ____ ____ ____ µg/dL

c. Ferritin: ____ ____ ____ ____ ng/mL

10. Is hepatic iron index available:

(Yes 1) (No 2)

12.

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+:

(Yes 1) (No 2)

15.

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:

(Yes 1) (No 2)

18.

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

a. Upper limit of normal: ____ ____ • ____ ____

mg/dL

b. Lower limit of normal: ____ ____ • ____ ____

mg/dL

F. Alpha-1 antitrypsin

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

____ ____–____ ____ ____–____ ____

day mon year

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: ____ ____ ____

mg/dL

20. A1AT phenotype *(if unknown record as "m")*

a. Pi Z heterozygote:

(Yes 1) (No 2)

b. Pi ZZ homozygote:

(Yes 1) (No 2)

21. A1AT deficiency *(physician judgment):*

(Yes 1) (No 2)

Elig

G. Autoantibody studies

22. Date of blood draw for autoantibody tests:

____ ____–____ ____ ____–____ ____

day mon year

Repeat if date is greater than 5 years prior to screening.

23. Antinuclear antibody (ANA):

Positive	(*1)
Negative	(2)

24.

a. If positive, ANA: 1/ ____ ____ ____ ____

**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 (2)
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 (2)
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:

Yes (1) No (2)
30.

27. Lymphocytotoxic antibody (LCA)*:

Positive (1)
Negative (2)
28.

a. If positive, LCA: 1/____ ____ ____ ____

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

Positive (1)
Negative (2)
29.

a. If positive, LKM1: 1/____ ____ ____ ____

29. Rheumatoid factor (RF)*:

Positive (1)
Negative (2)
30.

a. If positive, RF: ____ ____ ____ ____

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

H. Immunoglobulin levels

30. Are immunoglobulin levels available:

Yes (1) No (2)
35.

31. Date of blood draw for immunoglobulin levels:

____ ____–____ ____ ____–____ ____
day mon year

32. IgA: ____ ____ ____ mg/dL

33. IgG: ____ ____ ____ ____ mg/dL

34. IgM: ____ ____ ____ mg/dL

I. Other screening blood tests

35. 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.*

36. Thyroid stimulating hormone:

____ ____ • ____ ____ μU/mL

J. Administrative information

37. Study Physician PIN: ____ ____ ____

38. Study Physician signature:

_____

39. Clinical Coordinator PIN: ____ ____ ____

40. Clinical Coordinator signature:

_____

41. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

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

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code
(s1, n, or code for followup visit that is open):

____ ____ ____ ____

6. Form & revision: 1 t 1

7. Study: NAFLD Database 1

B. Liver biopsy

8. Date of biopsy:

____ ____–____ ____ ____–____ ____
day mon year

9. Was the liver tissue obtained using a 16-gauge or greater needle:

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

10. Was liver tissue obtained via a second pass:

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

11. Was the liver tissue obtained from a needle core biopsy *(as opposed to a wedge biopsy):*

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

C. Cryovial label

12. Attach duplicate cryovial label:

D. Flash freeze procedures

13. Was tissue flash frozen within 5 minutes of biopsy by placing in portable liquid nitrogen container:

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

15. ____

14. Explain what was done and why protocol was not followed:

_____

_____

_____

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

Yes (1) No (2)

17. ____

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

NAFLD Database

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

1. Center ID: ___ ___ ___ ___

2. Patient ID: ___ ___ ___ ___

3. Patient code: ___ ___ ___

4. Date of visit (date patient completed the form):

___ ___ - ___ ___ ___ - ___ ___
day month year

5. Visit code: ___ ___ ___ ___

6. Form & revision: **m a 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by the Clinical Coordinator after survey is completed).

8. How was the questionnaire completed:
Self-administered by patient/parent (1)
10.
Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that apply)*
a. Patient: (1)
b. Patient's mother or female guardian: (1)
c. Patient's father or male guardian: (1)
d. Other, *specify*: (1)
_____

10. Clinical Coordinator
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 3
6 to 8 days 4
9 or more days 5

13. How many times in the past 14 days have you done at least 20 minutes of light exercise that was not 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 3
6 to 8 days 4
9 or more days 5

14. During a normal week how many hours a day 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 sports or activities did you participate in on a competitive 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 5

What activities did you compete in?

_____

_____

_____

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

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

16. Check all activities that you did at least 10 times in the **PAST YEAR**. Do not include time spent in school physical education classes. Include all sport teams that you participated in during the last year.

( ) 01. Aerobics	( ) 02. Band/Drill Team	( ) 03. Baseball
( ) 04. Basketball	( ) 05. Bicycling	( ) 06. Bowling
( ) 07. Cheerleading	( ) 08. Dance Class	( ) 09. Football
( ) 10. Garden/Yard Work	( ) 11. Gymnastics	( ) 12. Hiking
( ) 13. Ice Skating	( ) 14. Roller Skating	( ) 15. Running and Exercise
( ) 16. Skateboarding	( ) 17. Snow Skiing	( ) 18. Soccer
( ) 19. Softball	( ) 20. Street Hockey	( ) 21. Swimming
( ) 22. Tennis	( ) 23. Volleyball	( ) 24. Water Skiing
( ) 25. Weight Training (Competitive)	( ) 26. Wrestling	( ) 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.

Activity Code #	Activity	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Months per Year	Days per Week	Minutes per Day
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __

17. Today's date: ________________________________

NAFLD Database

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.

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: f ____ ____ ____

6. Form & revision: m v 1

7. Study: NAFLD Database 1

B. Reason for completion of this form

8. Was the entire visit missed:

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

11. ____

C. Missed visit information

9. Reason for missed visit *(check all that apply)*

a. Patient was ill: ( ) (1)

b. Patient was temporarily away from area: ( ) (1)

c. Patient refused to return: ( ) (1)

d. Patient has permanently moved from the area: ( ) (1)

e. Unable to contact patient: ( ) (1)

f. Other *(specify):* ( ) (1)

_____
specify

10. Steps taken to avoid missing the visit *(check all that apply)*

a. Telephoned patient: ( ) (1)

b. Mailed reminder card: ( ) (1)

c. Other *(specify):* ( ) (1)

_____
specify

14. ____

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. 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)

l. 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. 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. Administrative information

14. Clinical Coordinator PIN: ___ ___ ___

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

___ ___–___ ___ ___–___ ___
day mon year

NAFLD Database

PA – Physical Activity

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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p a 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature: _____

9. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

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.

Circle one

10. Level of activity that best describes your usual non-recreational activity.

Vigorous or strenuous activity: 1
(involves heavy lifting, digging, handling heavy tools or equipment, or any other activity causing you to work up a sweat or get out of breath)

Moderate activity: 2
(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: 3
(involves sitting down with one hand movement, moderate one-arm work or light two-arm work, with occasional walking or standing such as office work, filing or sorting, or light or moderate housework)

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

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	Hours: _____ _____ 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	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: _____ _____
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.

NAFLD Database

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: p e 2

7. Study: NAFLD Database 1

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement:

____ ____ ____ • ____

b. Weight, 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
waist circumference

c. Units:

Inches (1)
Centimeters (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
hip circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
hip circumference

c. Units:

Inches (1)
Centimeters (2)

12. Triceps *(right arm, with elbow extended and arm relaxed; repeat skin fold measurements until you have two 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. Skin fold, 1st measurement:

____ ____ ____ • ____
mm

b. Skin fold, 2nd measurement:

____ ____ ____ • ____
mm

c. Mid-upper arm circumference, 1st measurement:

____ ____ • ____
arm circumference

d. Mid-upper arm circumference, 2nd measurement:

____ ____ • ____
arm circumference

e. Units for arm circumference:

Inches (1)
Centimeters (2)

13. Temperature
(Oral or other, as appropriate for age)

a. Degrees: ____ ____ ____ • ____

b. Scale:

Fahrenheit (1)
Centigrade (2)

14. Blood pressure

a. Systolic: ____ ____ ____
mmHg

b. Diastolic: ____ ____ ____
mmHg

15. Resting radial pulse: ____ ____ ____
beats/minute

16. Respiratory rate: ____ ____
breaths/minute

C. Examination findings

17. Skin:

Normal (1)
20.
Abnormal (2)

18. Acanthosis nigricans *(check only one):*

Absent *(not detectable on close inspection)* (0)

Present *(clearly present on close inspection, not visible to casual observer, extent not measurable)* (1)

Mild *(limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth)* (2)

Moderate *(extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front)* (3)

Severe *(extending anteriorly, > 6 inches in breadth, visible from front)* (4)

19. Other skin abnormality *(check all that apply)*

a. Jaundice: (1)
b. Palmar erythema: (1)
c. Spider angiomata: (1)
d. Other *(specify):* (1)

_____

e. None of the above: (1)

20. Head, eyes, ears, nose, throat:

Normal (1)
22.
Abnormal (2)

21. Abnormality of the head, eyes, nose, throat
(check all that apply)

a. Jaundice: (1)
b. Other *(specify):* (1)

_____
specify

22. Neck:

Normal (1)
23.
Abnormal (2)

_____
specify abnormality

23. Lymphatic:

Normal (1)
24. ____
Abnormal (2)

_____
specify abnormality

24. Chest and lungs:

Normal (1)
25. ____
Abnormal (2)

_____
specify

25. Heart:

Normal (1)
26. ____
Abnormal (2)

_____
specify abnormality

26. Abdomen:

Normal (1)
28. ____
Abnormal (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)
30. ____
Abnormal (2)

29. Abnormality of liver or spleen *(check all that apply)*

a. Hepatomegaly: (1)
(if checked, span from right midclavicular line):
____ ____ • ____
cm

b. Splenomegaly: (1)
c. Other *(specify):* (1)

_____
specify

30. Extremities:

Not performed (0)
32. ____
Normal (1)
32. ____
Abnormal (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)
e. Other *(specify):* (1)

_____
specify

32. Genitourinary/pelvis:

Not performed (0)
33. ____
Normal (1)
33. ____
Abnormal (2)

_____
specify

33. Nervous system:

Not performed (0)
35. ____
Normal (1)
35. ____
Abnormal (2)

34. Abnormality of the nervous system *(check all that apply):*

a. Mental status abnormal: (1)

b. Asterixis: (1)

c. Other *(specify):* (1)

_____
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: (1)

No, participant is 18 years old or older (2)

44.

No, participant had reached full sexual maturity *(Tanner stage 5 on all parameters at screening or for 2 consecutive visits)* (3)

44.

36. Is the patient female:

Yes (1) No (2)

40.

Male Tanner Staging

37. Genital stage: ____
1-5

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

39. Pubic hair stage: ____
1-5

44.

Female Tanner Staging

40. Breast stage: ____
1-5

41. Pubic hair stage: ____
1-5

42. Has menarche occurred:

Yes (1) No (2)

44.

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

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: f 0 2 4

6. Form & revision: p f 2

7. Study: NAFLD Database 1

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

10. Waist *(standing, at midpoint between highest point of iliac crest and lowest point of costal margin; repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

11. Hip *(standing, at fullest part of the hips; repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral or other as appropriate for age)*

a. Degrees: ____ ____ ____ • ____

b. Scale:
Fahrenheit: (1)
Centigrade: (2)

13. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

14. Resting radial pulse: ____ ____ ____ beats/minute

15. Respiratory rate: ____ ____ breaths/minute

C. Focused liver signs

16. Abnormality *(check all that apply)*

a. Ascites: (1)
b. Asterixis: (1)
c. Contractures: (1)
d. Hepatic encephalopathy: (1)
e. Hepatocellular carcinoma: (1)
f. Hepatomegaly: (1)

If Yes, span from right midclavicular line:

____ ____ • ____ cm

g. Hepatopulmonary syndrome: (1)
h. Hepatorenal syndrome: (1)
i. Jaundice: (1)
j. Muscle wasting: (1)
k. Palmar erythema: (1)
l. Pedal edema: (1)
m. Portal hypertension: (1)
n. Spider angiomata: (1)
o. Splenomegaly: (1)
p. Other, *(specify):* (1)

_____

q. None of the above (1)

D. Administrative information

17. Study Physician PIN: ____ ____ ____

18. Study Physician signature:

_____

19. Clinical Coordinator PIN: ____ ____ ____

20. Clinical Coordinator signature:

_____

21. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

NAFLD Database

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p q 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

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

SOCIAL 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

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. 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

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p r 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

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

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

SOCIAL 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

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. 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

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p s 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

Affix 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

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

SOCIAL 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

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. 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.

NAFLD Database

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p t 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

Affix label 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...)*	Never	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:	0	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:	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:	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with...)*	Never	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

Affix label here

Patient ID: __ __ __ __

Patient code: __ __ __

Visit code: __ __ __ __

***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.

NAFLD Database

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p v 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Interview in English (1)
Interview with translator (2)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
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 <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, 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	J	K	L

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 here

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.

PHYSICAL 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

Affix label here

Pt ID: __ __ __ __

Pt code: __ __ __

Visit code: __ __ __ __

ABOUT 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.

NAFLD Database

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p w 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day 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...)*	**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

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.

NAFLD Database

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p y 1**

7. Study: NAFLD Database 1

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

Affix label here

Patient ID: __ __ __ __

Patient code: __ __ __

Visit code: __ __ __ __

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

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 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

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.

NAFLD Database 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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **q f 1**

7. Study: NAFLD DATABASE 1

B. Administrative information
(To be completed by clinical center staff after survey is completed.)

8. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

9. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

Affix label here	
Patient ID:	__ __ __ __
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:

Circle 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?

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

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?

Activities	Circle one		
	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

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 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

16. How much bodily pain have you had during the past 4 weeks?

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

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

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.

NAFLD Database

RC - Rescreen in 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: r c 1

7. Study: NAFLD Database 1

B. NAFLD Database participation

8. Date in item 4 of original Database RG form: ____ ____–____ ____ ____–____ ____
day mon year

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature: _____

11. Date form reviewed: ____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

RG - Registration

Purpose: To register patients as candidates for enrollment in NAFLD Database and to assign a patient ID number. This is the first form completed for a NAFLD Database patient. The Registration Form must be the first form keyed, before any other NAFLD Database forms.

When: At first screening visit (s1).

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.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: r g 1

7. Study: NAFLD Database 1

B. Consent

8. Has the patient (or patient's guardian) signed the NAFLD Database informed consent statement:

Yes (1) No (2)

STOP

C. Information about patient

9. Date of birth:

____ ____ – ____ ____ ____ – ____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

10. Age at last birthday: ____ ____
years

11. Gender:

Male (1)
Female (2)

12. Ethnic category *(show the patient/parent 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)

14.

13. What describes your Hispanic, Latino, or Latina origin best *(show the patient/parent Flash Card #1 and ask the respondent 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

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)*

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 *(check only one):*

Continental US (includes Alaska) or Hawaii (1)
Other, *(specify):* (2)

_____
specify

16. Highest educational level achieved by patient *(show the patient/parent Flash Card #3 and ask the respondent to pick the category that describes the patient best; check only one):*

- Never attended school (0)
- Kindergarten, pre kindergarten, or younger (1)
- Grades 1 to 5 (2)
- Grades 6-8 (3)
- Grades 9-11 (4)
- Completed high school (5)
- Some college or post high school education or training (6)
- Bachelor's degree or higher (7)

17. Is the patient currently employed:

Yes (1) No (2)

20.

18. What is the patient's current occupation:

_____
specify occupation

19. About how many hours does the patient work each week: ___ ___
hours

20. Which of the following categories best characterizes the patient's occupational history *(show the patient/parent Flash Card #4 and ask the respondent to pick the category that describes the patient best; check only one):*

- Never employed (0)
- Laborer (1)
- Clerical (2)
- Professional (3)
- Homemaker (4)
- Other, *(specify):* (5)

_____
specify

21. Marital status of the patient *(show the patient/parent Flash Card #5 and ask the respondent to pick the category that describes the patient best; check only one):*

- Single, never married (1)
- Married or living in marriage-like relationship (2)
- Separated, divorced, or annulled (3)
- Widowed (4)

22. Combined annual income before taxes of all members of patient's household *(show the patient/parent Flash Card #6 and ask the 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)

23. Is the patient under age 18:

Yes (1) No (2)

28.

24. Current age of patient's mother, stepmother, or female guardian *(show patient/parent Flash Card #7; check only one):*

- Not applicable (mother is deceased or patient has no stepmother or female guardian) (0)
- 19 or younger (1)
- 20-29 years (2)
- 30-39 years (3)
- 40-49 years (4)
- 50-59 years (5)
- 60 years or older (6)

25. Highest educational level achieved by patient's mother, stepmother, or female guardian *(show patient/parent Flash Card #8; if education of mother or female guardian is unknown, record as "n"; check only one):*

- Never attended school (0)
- Did not complete high school (1)
- Completed high school (2)
- Some college or post high school education or training (3)
- Bachelor's degree or higher (4)

26. Current age of patient's father, stepfather, or male guardian *(show patient/parent Flash Card #7; check only one):*

Not applicable (father is deceased or patient has no stepfather or male guardian)	(0)
19 or younger	(1)
20-29 years	(2)
30-39 years	(3)
40-49 years	(4)
50-59 years	(5)
60 years or older	(6)

27. Highest educational level achieved by patient's father, stepfather, or male guardian *(show patient/parent Flash Card #8; if education of father or male guardian is unknown, record as "n"; check only one):*

Never attended school	(0)
Did not complete high school	(1)
Completed high school	(2)
Some college or post high school education or training	(3)
Bachelor's degree or higher	(4)

D. Source of patient

(clinic staff should pick the best description of the source of the patient)

28. 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	(08)
Obesity clinic	(09)
Pediatric clinic	(10)
Pediatric weight disorders clinic	(11)
Primary care clinic	(12)
Self referral	(13)
Other, *(specify):*	(14)

_____
specify

E. Previous registration in a NASH CRN study

29. Has the patient ever been assigned an ID number in a NASH CRN study:

Yes (1) No (2)

33. ___

30. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

a. PIVENS:	(1)
b. TONIC:	(1)
c. Other, *(specify):*	(1)

_____
specify

31. ID Number previously assigned to patient *(record patient ID in item 2):*

___ ___ ___ ___

32. Code previously assigned to patient *(record patient code in item 3):*

___ ___ ___

34. ___

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.

CCCC ####, zzz

G. Administrative information

34. Clinical Coordinator PIN: ___ ___ ___

35. Clinical Coordinator signature:

_____

36. Date form reviewed:

___ ___ – ___ ___ ___ – ___ ___
day mon year

NAFLD Database

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.

A. Center, patient and visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code *(s1 or code for followup visit that is currently open):*

____ ____ ____ ____

6. Form & revision: s d 3

7. Study: NAFLD Database 1

B. Surgical pathology report

8. Was a copy of the surgical pathology report for the biopsy obtained:

Yes (+ 1) No (* 2)

26. ____

+ 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.*

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 (3)

C. Biopsy specimens and stained slides at the clinical center

10. Was a sample of liver tissue obtained for banking:

Yes (*1) No (2)

** If Yes, complete the Liver Tissue Banking (LT) form*

11. Is this visit s1 *(ie, a patient currently in screening*):

Yes (1) No (2)

14.

12. Were you able to obtain stained slides from this biopsy for local evaluation and were they adequate for scoring:

Yes (+1) No (*2)

26.

+ 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:

Yes (1) No (2)

17.

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: ____ ____ 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

E. Stained slides to be sent to the DCC

17. Is the institution's H & E stained slide to be sent to the DCC:

Yes (1) No (2)

20.

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:

Yes (1) No (2)

20. Is the institution's Masson's trichrome stained slide to be sent to the DCC:

Yes (1) 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:

(Yes 1) (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 1) (No 2)

26. ____

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 (1)

26. ____

Other, *(specify):* (2)

_____
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.

F. Administrative information

26. Clinical Coordinator PIN: ____ ____ ____

27. Clinical Coordinator signature:

_____

28. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

SE - Most Recent Prior Liver Biopsy Materials Documentation

Purpose: To document whether the **most recent 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 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 visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code s 1 ____ ____

6. Form & revision: s e 1

7. Study: NAFLD Database 1

B. Surgical pathology report

8. Was a copy of the surgical pathology report for the biopsy obtained:

Yes (+ 1) No (* 2)

24. ____

+ 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.*

9. Date of biopsy specified on the surgical pathology report:

____ ____–____ ____ ____–____ ____
day mon year

C. Stained slides at the clinical center

10. Were you able to obtain stained slides from this biopsy for local evaluation and were they adequate for scoring:

Yes (+ 1) No (* 2)

24. ____

+ Continue with this form and also complete form HE.

** This biopsy cannot be used for the NAFLD Database.*

11. 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

12. Are unstained slides available for sending to the DCC:

(Yes 1) (No 2)

15. ____

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: ____ ____ 01-60

b. Slide sequence number: ____ ____ 01-60

c. 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

E. Stained slides to be sent to the DCC

15. Is the institution's H & E stained slide to be sent to the DCC:

(Yes 1) (No 2)

18. ____

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:

(Yes 1) (No 2)

18. Is the institution's Masson's trichrome stained slide to be sent to the DCC:

(Yes 1) (No 2)

21. ____

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:

(Yes 1) (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 1) (No 2)

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 (2)

23. Which pathology department did these slides come from *(check only one):*

NASH CRN clinical center's pathology department (1)

24. ____

Other, *(specify):* (2)

_____ 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.

F. Administrative information

24. Clinical Coordinator PIN: ____ ____ ____

25. Clinical Coordinator signature:

_____

26. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database

SF - Next Most Recent Prior Liver Biopsy Materials Documentation

Purpose: To document whether the **next most recent 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 visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code s 1 ____ ____

6. Form & revision: s f 1

7. Study: NAFLD Database 1

B. Surgical pathology report

8. Was a copy of the surgical pathology report for the biopsy obtained:

Yes (+1) No (*2)

24.

+ 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.*

9. Date of biopsy specified on the surgical pathology report:

____ ____–____ ____ ____–____ ____
day mon year

C. Stained slides at the clinical center

10. Were you able to obtain stained slides from this biopsy for local evaluation and were they adequate for scoring:

Yes (+1) No (*2)

24.

+ Continue with this form and also complete form HG.

** This biopsy cannot be used for the NAFLD Database.*

11. 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

12. Are unstained slides available for sending to the DCC:

(Yes 1) (No 2)

15. ____

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: ____ ____ 01-60

b. Slide sequence number: ____ ____ 01-60

c. 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

E. Stained slides to be sent to the DCC

15. Is the institution's H & E stained slide to be sent to the DCC:

(Yes 1) (No 2)

18. ____

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:

(Yes 1) (No 2)

18. Is the institution's Masson's trichrome stained slide to be sent to the DCC:

(Yes 1) (No 2)

21. ____

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:

(Yes 1) (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 1) (No 2)

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 (2)

23. Which pathology department did these slides come from *(check only one):*

NASH CRN clinical center's pathology department (1)

24. ____

Other, *(specify):* (2)

_____ 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.

F. Administrative information

24. Clinical Coordinator PIN: ____ ____ ____

25. Clinical Coordinator signature:

_____

26. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

Keyed: ( )

NAFLD Database

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of notification of intent to transfer:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: t n 1

7. Study: NAFLD Database 1

B. Last followup visit information

8. Date of last followup visit:

____ ____–____ ____ ____–____ ____
day mon year

9. Visit ID code of last completed followup visit:

____ ____ ____ ____

10. Have cryovial and slide labels been sent to the adopting center:

(Yes 1) (No *2)

* Send the cryovial and slide labels to the adopting center.

C. Current center administrative information

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

12. Clinical coordinator ID: ____ ____ ____

13. Clinical coordinator signature:

_____

D. Adopting center, patient and visit identification

14. Adopting center ID: ____ ____ ____ ____

15. Patient ID *(must be same as in Section A):*

____ ____ ____ ____

16. Patient code *(must be same as in Section A):*

____ ____ ____

17. Expected date of first followup visit at adopting center:

____ ____–____ ____ ____–____ ____
day mon year

18. Visit ID code for expected first followup visit at adopting center:

____ ____ ____ ____

Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.

E. Adopting center administrative information

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

20. Clinical coordinator ID: ____ ____ ____

21. Clinical coordinator signature:

_____

Fax form to the DCC. The DCC will key the TN form.

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
BC	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 – 1st Reading
HT	Steatohepatitis Determination –2nd Reading
IE	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

PIVENS

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, 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.

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: **s** **1** _____ _____
6. Form & revision: **a** **d** **1**
7. Study: PIVENS 2

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. Clinical Coordinator PIN: _____ _____ _____
9. Clinical Coordinator signature: _____
10. 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 1-9 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
(0)	(1)	(2)	(3)	(4)

→ **21.**

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?

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

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
(0)	(1)	(2)	(3)	(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
(0)	(1)	(2)	(3)	(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
(0)	(1)	(2)	(3)	(4)

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

No	Yes, but not in the last year	Yes, during the last year
(0)	(1)	(2)

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
(0)	(1)	(2)

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 **serious** (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) **and unexpected** (not included in the PIVENS protocol) adverse event that, in the opinion of the investigators, **is thought to be associated** with PIVENS study drugs.

When: As needed. The AN form should be used **only** for reporting of a **serious and unexpected** 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 **does not** 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, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____
If report not associated with a visit, fill in "n."

6. Form & revision: a n 2

7. Study: PIVENS 2

B. Participant information

8. Date randomized in PIVENS:

____ ____–____ ____ ____–____ ____
day mon year

9. Gender:

Male (1)
Female (2)

10. Age at time of event: ____ ____
years

11. Is the patient currently receiving the pioglitazone-series study drug:

Yes (1) No (2)

12. Is the patient currently receiving the vitamin E-series study drug:

Yes (1) No (2)

13. Summarize the patient's history of treatment with PIVENS study drugs *(eg, how long has patient been on study drugs, have there been any treatment interruptions):*

C. Adverse event description

14. Is the adverse event associated with PIVENS study drugs both **serious** and **unexpected**:

(Yes *1) (No †2)

**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	(3)
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:

____ ____–____ ____ ____–____ ____
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 *1) (No 2)

**Attach a copy of the institutional pathology report to the AN form.*

23. Did the event result in significant sequelae:

(Yes 1) (No 2) **24.**

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 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):*

_____

_____

26. Severity grade *(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 other PIVENS forms to report adverse events of Grade 1 (mild) or Grade 2 (moderate); call the DCC if unsure what to do):*

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)

_____

_____

_____

g. None of the above	(1)

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

Resolved	(1)
Active	(2)
	30.
Unknown	(3)
	30.

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:

_____

35. 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.

PIVENS

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b c 1

7. Study: PIVENS 2

B. Check on consent

8. Did the patient consent to blood draw for DNA extraction:

Yes (1) No (*2)

STOP

** You cannot proceed until you get consent.*

9. Did the patient previously provide blood for DNA banking in the NAFLD Database:

Yes (1) No (2)

15.

C. Specimen for Genetics Repository

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 the NIDDK Genetics Repository.

10. Was blood collected for the NIDDK Genetics Repository:

Yes (1)

11.

No, *(specify):* (2)

_____
specify

15.

11. Date and time of blood draw

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) am (2) pm
hour minute

12. Number of 10 mL EDTA tubes: ____

13. Form copy of tube labels:

PIVENS Form BC
Pt: ccc- 9999, xyz
Gender
Age, yrs.: XX

14. Phlebotomist:

_____
print name

D. Administrative information

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed *(date food questionnaire booklet is completed):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b d 1

7. Study: PIVENS 2

B. Administration of food questionnaire

8. Form copy of label applied to food questionnaire:

PIVENS Form BD
Pt: 9999,xyz
Visit: vvvv
Date: _____

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature:

_____

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon 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 ⚠C is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for PIVENS. If ⊘PIVENS 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, 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: s 1 ____ ____

6. Form & revision: b g 3

7. Study: PIVENS 2

B. Family history

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

Yes (1) No (2)
10.

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

a. Alcohol related liver disease: (1)
b. Viral hepatitis: (1)
c. Alpha-1 antitrypsin deficiency: (1)
d. Wilson's disease: (1)
e. Glycogen storage disease: (1)
f. Iron overload: (1)
g. Fatty liver disease *(NAFLD, NASH):* (1)
h. Primary liver cancer: (1)
i. Type of liver disease unknown: (1)
j. Other *(specify):* (1)

_____
specify

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

Yes (1) No (2)
12.

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

Yes (1) 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)

14. Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:

Yes (1)
No (2)
Don't know (3)

15. Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood fat:

Yes (1)
No (2)
Don't know (3)

C. NASH history

16. Date patient was first diagnosed with nonalcoholic steatohepatitis (NASH):

____ ____–____ ____ ____–____ ____
day mon year

17. What prompted the evaluation for NASH *(check all that apply)*

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)
e. Other *(specify):* (1)

_____
specify

18. What procedures/tests supported this first diagnosis *(check all that apply)*

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

_____
specify

D. Weight history

19. What was the patient's birthweight:

____ ____–____ ____
lbs oz

20. *Review flashcard 9.* 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)
No or minimal change (6)

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

24. What is the least the patient has 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:

Yes (1) No (2)

28.

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:

Yes (1) No (2)

30.

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:

Yes (1) No (2)

32.

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:

Never (1)

37.

In the past but not anymore (2)
Currently smokes cigarettes (3)

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):*

Yes (1) No (2)

37.

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

F. Menstrual history

37. Is the patient female:

Yes (1) No (2)

42.

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

40. Is patient post-menopausal:

Yes (1) No (2)

42.

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 diagnosis)*

42. 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: C (1)

b. Diabetes type 2: C (1)

c. Gestational diabetes *(diabetes of pregnancy):* (1)

d. Hepatitis B: C (1)

e. Hepatitis C: C (1)

f. Autoimmune hepatitis: C (1)

g. Autoimmune cholestatic liver disorder (PBC or PSC): C (1)

h. Wilson's disease: C (1)

i. Alpha-1-antitrypsin (A1AT) deficiency: C (1)

j. Iron overload: C (1)

k. Drug induced liver disease: C (1)

l. Gilbert's syndrome: (1)

m. Esophageal or gastric varices on endoscopy: C (1)

n. Bleeding from varices: C (1)

o. Other gastrointestinal bleeding: (1)

p. Biliary diversion: C (1)

q. Ascites: C (1)

r. Edema: (1)

s. Hepatic encephalopathy: C (1)

t. Portal hypertension: C (1)

u. Hepatorenal syndrome: C (1)

v. Hepatopulmonary syndrome: C (1)

w. Short bowel syndrome: C (1)

x. Hemophilia *(bleeding disorder):* C (1)

y. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

z. Endocrine disease *(hormonal abnormality):* (1)

aa. Hepatocellular carcinoma: C (1)

ab. Other malignancy *(cancer):* C (1)

ac. Human immunodeficiency virus (HIV): C (1)

ad. Peripheral neuropathy: (1)

ae. Seizure disorder or epilepsy: (1)

af. Drug allergies: (1)

ag. Hypothyroidism: (1)

ah. Hypertension: (1)

ai. Cerebrovascular disease: (1)

aj. Dysbetalipoproteinemia: C (1)

ak. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

al. Pancreatitis: (1)

am. Cholelithiasis: C (1)

an. Coronary artery disease: C (1)

ao. Congestive heart failure: (1) C

ap. Elevated uric acid such as gout: (1)

aq. Kidney disease: (1)

ar. Polycystic ovary syndrome: (1)

as. Sleep apnea *(not breathing during sleep):* (1)

at. Dermatologic disorders: (1)

au. Myopathy: (1)

av. Myositis: (1)

aw. Major depression: (1)

ax. Schizophrenia: (1)

ay. Bipolar disorder: (1)

az. Obsessive compulsive disorder: (1)

ba. Severe anxiety or personality disorder: (1)

bb. Substance abuse: (1) C

bc. None of the above: (1)

43. Has the patient ever had bariatric surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1) C

b. Jejunoileal *(or other intestinal)* bypass: (1) C

c. Biliopancreatic diversion: (1) C

d. Other GI or bariatric surgery *(specify):* (1)

_____

e. None of the above: (1)

44. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) Elig No (2)

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

Yes (1) No (2)

45. Has the patient received total parenteral nutrition (TPN) in the past 12 months:

Yes (1) Elig No (2)

46. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) Elig No (2)

H. Drugs historically associated with NAFLD

47. Has the patient used any of the following in the past 2 years

a. Amiodarone (Cordarone, Pacerone): (1)

b. Demeclocycline (Declomycin): (1)

c. Divalproex (Depakote): (1)

d. Doxycycline (Monodox): (1)

e. Methotrexate (Rheumatrex): (1)

f. Minocycline (Dynacin, Minocin): (1)

g. Oxytetracycline (Terramycin): (1)

h. Tetracycline (Achromycin): (1)

i. Valproate sodium (Depacon): (1)

j. Valproic acid (Depakene): (1)

k. Other known hepatotoxin *(specify):* (1)

_____

l. None of the above: (1)

48. Were any of the items on 47a-k checked:

Yes (*1) C No (2)

**Caution: Use of any of these drugs for more than 2 consecutive weeks in the past 2 years is exclusionary.*

49. Has the patient taken any systemic corticosteroids in the past 2 years *(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)

50. Were any of the items 49a-k checked:

Yes (* 1) → C No (2)

**Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past 2 years is exclusionary.*

51. Has the patient taken any estrogen, progestin, anabolic steroids, hormone replacement therapy, or selective estrogen receptor modulators in the past 2 years *(check all that apply):*

a. Boldenone undecylenate (Equipoise): (1)

b. Conjugated estrogen (Premarin/Prempro): (1)

c. Diethylstilbestrol and methyltestosterone (Tylosterone): (1)

d. Esterified estrogen (Estratab, Menest): (1)

e. Estradiol (Estrace): (1)

f. Ethinyl estradiol (Estinyl): (1)

g. Fluoxymesterone (Android-F, Halotestin): (1)

h. Levonorgestrel (Norplant): (1)

i. Medroxyprogesterone (Cycrin, Provera): (1)

j. Megestrol (Megace): (1)

k. Methandrostenolone (Dianabol): (1)

l. Methyltestosterone (Android): (1)

m. Nandrolone (Deca-Durabolin, Durabolin, Hybolin Decanoate, Kabolin): (1)

n. Norethindrone (Micronor): (1)

o. Norgestrel (Ovrette): (1)

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): (1)

t. Raloxifene (Evista): (1)

u. Stanzolol (Winstrol): (1)

v. Tamoxifen (Nolvadex): (1)

w. Testosterone (Depo-Testosterone): (1)

x. Other, *(specify):* (1)

_____

y. Other, *(specify):* (1)

_____

z. None of the above: (1)

52. Were any of the items 51a-y checked:

Yes (* 1) → C No (2)

**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):

Yes (1) → Elig No (2)

54. Has the patient used any antidiabetic medications in the past 12 months *(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): (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: (1)

55. Were any of the items 54a-p checked:

Yes (* 1) → C No (2)

**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): (1)

b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)

c. Metformin: (1)

d. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)

e. S-adenylmethionine (SAM-e): (1)

f. Milk thistle: (1)

g. Probiotics *(any form):* (1)

h. Gemfibrozil (Gen-Fibro, Lopid): (1)

i. Other *(specify):* (1)

_____
specify

j. None of the above: (1)

57. Were any of the items in 56a-h checked:

Yes (* 1) No (2)

C

**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): (1)

b. Infliximab (Remicade): (1)

c. Other, *(specify):* (1)

_____

d. None of the above: (1)

59. Were any of the items 58a-c checked:

Yes (* 1) No (2)

C

**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:

Yes (1) No (2)

61. Has the patient taken any vitamin E (either as a supplement or in a multivitamin) in the past 12 months):

Yes (1) No (2)

63.

62. Was/Is the dose of vitamin E greater than 100 IU/day:

Yes (* 1) No (2)

C

**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:

Yes (1) No (* 2)

Elig

**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:

Yes (1) No (2)

Elig

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): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Other, *(specify):* (1)

_____

e. None of the above: (1)

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): (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)

j. Simvastatin (Zocor): (1)

k. Other, *(specify):* (1)

_____

l. None of the above: (1)

67. Were any of the items 66a-k checked:

Yes (* 1) → C No (2)

**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): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

c. Methamphetamine hydrochloride (Desoxyn, Gradumet): (1)

d. Orlistat (Xenical): (1)

e. Phendimetrazine tartrate (Adipost, Bontril): (1)

f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): (1)

g. Sibutramine hydrochloride monohydrate (Meridia): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

69. Were any of the items 68a-i checked:

Yes (* 1) → C No (2)

**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 cardiovascular or antihypertensive medications in the past 12 months that have not already been reported on this form *(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)
l. 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)
y. Verapamil (Calan): (1)
z. Other, *(specify):* (1)

_____

aa. Other, *(specify):* (1)

_____

ab. None of the above: (1)

71. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 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):* (1)

_____

k. Other, *(specify):* (1)

_____

l. 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)*

a. Darvocet: (1)
b. Esgic - Plus: (1)
c. Fioricet: (1)
d. Lorcet: (1)
e. Lortab: (1)
f. Norco: (1)
g. Percocet: (1)
h. Talacen: (1)
i. Tylenol #3: (1)
j. Tylenol #4: (1)
k. Tylox: (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)

75. Has the patient taken any allergy or asthma medications in the past 12 months that have not already been reported on this form *(check all that apply)*

a. Albuterol: (1)
b. Beclomethasone dipropionate (Beclovent, Vanceril): (1)
c. Budesonide (Pulmicort, Rhinocort): (1)
d. Fluticasone propionate (Flonase, Flovent): (1)
e. Loratadine (Claritin): (1)
f. Mometasone furoate (Nasonex): (1)
g. Triamcinolone acetonide (Azmacort, Nasacort): (1)
h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

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)
l. 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)

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): (1)

d. Disulfiram (Antabuse): (1)

e. Hydroxyzine pamoate (Vistaril): (1)

f. Naltrexone hydrochloride (Revia): (1)

g. Other, *(specify):* (1)

_____

h. None of the above: (1)

79. Were any of the items 78a-g checked:

Yes (* 1) → C No (2)

**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:

Yes (1) No (2) → **84.**

81. Are you currently pregnant:

Yes (1) → Elig No (2)

82. Are you currently breast feeding:

Yes (* 1) → C No (2)

**Caution: Patient cannot be breastfeeding at time of randomization.*

83. Are you willing to use effective birth control methods during PIVENS *(ask only females):*

Yes (1) → Elig No (2)

N. Administrative information

84. Study Physician PIN: ____ ____ ____

85. Study Physician signature:

_____

86. Clinical Coordinator PIN: ____ ____ ____

87. Clinical Coordinator signature:

_____

88. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 consent to serum banking for future research		Patient who does NOT consent to serum banking for future research	
Visit	No. of 4.5 mL CTAD tubes to fill	No. of plasma aliquots	No. of 10 mL SST tubes to fill	No. of serum aliquots	No. of 10 mL SST tubes to fill	No. of serum 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

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b p 1

7. Study: PIVENS 2

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)
24. ___
No, other reason *(specify):* (3)
24. ___

_____
specify other reason

9. Date and time of blood draw

a. Date:

___ ___–___ ___ ___–___ ___
day mon year

b. Time:

___ ___ : ___ ___ (1) (2)
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):*

Yes (1) No (2)
13. ___

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 1
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

PIVENS Serum 2
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

PIVENS Serum 3
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

PIVENS Serum 4
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

a. Date:

___ ___–___ ___ ___–___ ___
day mon year

b. Time:

___ ___ : ___ ___ (1) (2)
hour minute am pm

17. Number of aliquots of plasma *(if this was not a plasma banking visit, record "0")*:

___

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):

Serum aliquot #00 label	Plasma aliquot #00 label

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:
____ ____:____ ____ ($_1$) ($_2$)
hour minute am pm

22. Number of cryovials frozen: ____ ____

23. Technician:

_____
print name

E. Administrative information

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: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: c g 1

7. Study: PIVENS 2

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:

(Yes 1) (No 2)

9. Does the patient consent to future genetic research on NASH by this study or other study investigators:

(Yes 1) (No 2)

10. Does the patient consent to future genetic research not related to NASH by this study or other study investigators:

(Yes 1) (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 NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):*

(Yes 1) (No 2)

C. Consent for serum, plasma, and liver tissue storage for future research

13. Is this a patient at Duke or CWRU:

(Yes 1) (No 2)

15.

14. Does the patient consent to have his/her serum, plasma, and liver tissue stored for future research:

(Yes 1) (No 2)

D. 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

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.

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: f 1 2 0

6. Form & revision: c o 1

7. Study: PIVENS_2

B. Database participation

8. Does the patient wish to re-enter or join the NAFLD Database:

(Yes 1) (No 2)

11.

9. Has the patient signed the latest version of the NAFLD Database informed consent:

(Yes 1) (No * 2)

STOP

** Patient must sign the informed consent*

10. Was the patient enrolled in the NAFLD Database previously:

(Yes * 1) (No + 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 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 follow-up 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of biopsy:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: c r 1

7. Study: PIVENS 2

B. Central reading

8. Date of central reading:

____ ____–____ ____ ____–____ ____
day mon year

9. Which stained slides are available for review *(check all that apply)*

a. H & E: (1)

b. Masson's trichome: (1)

c. Iron: (1)

d. Other *(specify):* (1)

_____

10. Biopsy length: ____ ____ mm

11. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5% (0)
5-33% (1)
34-66% (2)
> 66% (3)

b. Location:

Zone 3 (0)
Zone 1 (1)
Azonal (2)
Panacinar (3)

c. Microvesicular steatosis, contiguous patches:

Not present (0)
Present (1)

12. Fibrosis stage *(Masson's trichrome stain)*

0: None (0)
1a: Mild, zone 3, perisinusoidal (requires trichome) (1)
1b: Moderate, zone 3, perisinusoidal (easily seen on H&E) (2)
1c: Portal/periportal only (3)
2: Zone 3 and periportal, any combination (4)
3: Bridging (5)
4: Cirrhosis (6)

13. Inflammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

0 (0)
< 2 under 20x mag (1)
2-4 under 20x mag (2)
> 4 under 20x mag (3)

b. Micrognanulomas seen:

Yes (1) No (2)

c. Large lipogranulomas seen:

Yes (1) No (2)

d. Amount of portal, chronic inflammation:

0: None (0)
1a: Mild (1)
1b: More than mild (2)

14. Liver cell injury

a. Ballooning:

None (0)
Few (1)
Many (2)

b. Acidophil bodies:

Rare (0)
Many (1)

c. Pigmented macrophages:

Rare/absent (0)
Many (1)

d. Megamitochondria:

Rare/absent (0)
Many (1)

15. Mallory bodies

Rare/absent (0)
Many (1)

16. Glycogen nuclei:

Rare/absent (0)
Many (1)

17. Iron stain

a. Hepatocellular grade:

Absent or barely discernible, 40x (0)
Barely discernible granules, 20x (1)
Discrete granules resolved, 10x (2)
Discrete granules resolved, 4x (3)
Masses visible by naked eye (4)

b. Hepatocellular iron distribution:

Periportal (0)
Periportal and midzonal (1)
Panacinar (2)
Zone 3 or nonzonal (3)

c. Sinusoidal lining cell iron grade:

None (0)
Mild (1)
More than mild (2)

d. Sinusoidal lining cell iron distribution:

Large vessel endothelium only (0)
Portal/fibrous bands only, but more than just in large vessel endothelium (1)
Intraparenchymal only (2)
Both portal and intraparenchymal (3)

18. Is this steatohepatitis:

No (1)
Suspicious/borderline/indeterminate (2)
Yes, definite (3)

19. Is cirrhosis present:

Yes (1) No (2) → **21.**

20. In the committee's opinion, is this **cryptogenic cirrhosis**:

Yes (1) No (2)

21. Other features *(check all that apply)*

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)

22. Other comments *(specify):*

_____

_____

_____

_____

_____

C. Administrative information

23. Data Coordinating Center personnel signature:

_____

24. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: d d 1

7. Study: PIVENS_2

B. DEXA scan information

8. Did the patient have a whole body dual energy x-ray absorptiometry (DEXA) scan:

Yes (1) No (2)

10. ____

9. Reason why DEXA scan was not performed *(check all that apply)*

a. Patient is heavier than the allowed weight: (1)

b. Scanner is broken: (1)

c. Other *(specify):* (1)

_____
specify

17. ____

10. DEXA scanner used:

Hologic QDR 4500A (1)
Hologic QDR 4500W (2)
Hologic New Discovery Series 12.3 (3)
Hologic Delphi QDR Series (4)
Hologic Delphi W (5)
Lunar Prodigy (6)
Other *(specify)* (7)

_____
specify make & model number

C. DEXA results summary

11. Lumbar spine BMD: ____ • ____ ____ ____
g/cm2

12. Pelvis BMD: ____ • ____ ____ ____
g/cm2

13. Subtotal bone mineral density: ____ • ____ ____ ____
g/cm2

14. Total bone mineral density: ____ • ____ ____ ____
g/cm2

15. Total T-score: ____ ____ • ____
+/-

16. Total Z-score (if available): ____ ____ • ____
+/-

D. Administrative information

17. Clinical Coordinator PIN: ____ ____ ____

18. Clinical Coordinator signature:

_____

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: d r 1

7. Study: PIVENS_2

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Health care provider or NASH CRN staff: (1)
d. Newspaper: (1)
e. Funeral parlor/home: (1)
f. Medical record: (1)
g. Medical examiner: (1)
h. Coroner: (1)
i. Other *(specify):* (1)

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

11. Cause of death
(Study Physician: use whatever knowledge you have and your best medical judgment to best characterize the cause of death; check only one):

Heart disease (1)
Stroke (2)
Liver disease (3)
Malignancy (4)
Other *(specify):* (5)

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: d x 2

7. Study: PIVENS 2

B. DEXA scan information

8. Did the patient have a whole body dual energy x-ray absorptiometry (DEXA) scan:

(Yes 1) (No 2)

10. ____

9. Reason why DEXA scan was not performed *(check all that apply)*

a. Patient is heavier than the allowed weight: (1)

b. Scanner is broken: (1)

c. Other *(specify):* (1)

_____
specify

14. ____

10. DEXA scanner used:

Hologic QDR 4500A	(1)
Hologic QDR 4500W	(2)
Hologic New Discovery Series 12.3	(3)
Hologic Delphi QDR Series	(4)
Hologic Delphi W	(5)
Lunar Prodigy	(6)
Other *(specify)*	(7)

_____
specify make & model number

C. DEXA results summary

11. Date of DEXA scan:

____ ____–____ ____ ____–____ ____
day mon year

12. Trunk % fat
(if your scanner reports both tissue % fat and region % fat, record region % fat on this report):

____ ____ • ____
%

13. Total % fat
(if your scanner reports both tissue % fat and region % fat, record region % fat on this report):

____ ____ • ____
%

D. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 Elig 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.

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: r z ____ ____

6. Form & revision: e c 1

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:

( ) Yes 1 → Elig
( ) No 2

9. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her *(past and current)* alcohol intake:

( ) Yes 1
( ) No 2 → Elig

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:

( ) Yes 1
( ) No 2 → Elig

C. Cirrhosis exclusion

11. Clinical cirrhosis evaluation

a. Does the patient have varices or ascites and does the physician judge that the patient has cirrhosis:

( ) Yes (1) ( ) No (2) → Elig

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):*

( ) Yes (1) ( ) No (2) → Elig

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:

( ) Yes (1) ( ) No (2) → Elig

b. In the Study Physician's judgment, does the patient have a history of autoimmune hepatitis:

( ) Yes (1) ( ) No (2) → Elig

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:

( ) Yes (1) ( ) No (2) → Elig

14. Does the patient have known primary sclerosing cholangitis and suggestive liver histology:

( ) Yes (1) ( ) No (2) → Elig

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:

( ) Yes (1) ( ) No (2) → Elig

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):*

( ) Yes (1) ( ) No (2) → Elig

17. Hemochromatosis

a. Does the patient have a history of hemochromatosis:

( ) Yes (1) ( ) No (2) → Elig

b. Does the patient have a iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:

( ) Yes (1) ( ) No (2) → Elig

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:

( ) Yes (1) ( ) No (2) → Elig

b. Known bile duct obstruction:

( ) Yes (1) ( ) No (2) → Elig

c. Suspected or proven liver cancer:

( ) Yes (1) ( ) No (2) → Elig

d. Any other type of liver disease other than NASH that warrants exclusion from the trial:

( ) Yes (1) ( ) No (2) → Elig

E. Other medical exclusions

19. History of diabetes mellitus:

(Yes 1) (No 2)

20. History of bariatric surgery *(jejunoileal bypass or gastric weight loss surgery:*

(Yes 1) (No 2)

21. History of biliary diversion:

(Yes 1) (No 2)

22. Known positivity for antibody to Human Immunodeficiency Virus (HIV):

(Yes 1) (No 2)

23. Known heart failure of New York Heart Association class 2, 3, or 4:

(Yes 1) (No 2)

24. Inability to safely undergo liver biopsy:

(Yes 1) (No 2)

25. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the 2 years prior to screening:

(Yes 1) (No 2)

26. Use of antidiabetic drugs in the 3 months prior to randomization:

(Yes 1) (No 2)

27. Use of antiNASH drugs in the 3 months prior to randomization:

(Yes 1) (No 2)

28. Use of a VARIABLE dose of any statins or fibrates in the 3 months prior to randomization:

(Yes 1) (No 2)

29. Use of antiobesity drugs in the 3 months prior to randomization:

(Yes 1) (No 2)

30. Use of Vitamin E at a dose greater than 100 IU/day:

(Yes 1) (No 2)

31. Known active, serious medical disease with a likely life-expectancy less than 5 years:

(Yes 1) (No 2)

32. Known active substance abuse, such as alcohol or inhaled or injection drugs in the year prior to screening:

(Yes 1) (No 2)

33. Other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study:

(Yes 1) (No 2)

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):*

( ) Yes (1) ( ) No (2) → Elig

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:

( ) Yes (1) ( ) No (2)*

44.

**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:

Yes ( ) (1) → **44.**

No ( ) (2)

Task not run because patient is known to be ineligible ( ) (3) → **44.**

37. Does the patient feel well today:

( ) Yes (1) ( ) No (2)* → STOP

**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:

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

42.

39. Is the patient of childbearing potential:

( ) Yes (1)* ( ) No (2)

41.

**Administer pregnancy test.*

40. Is the patient pregnant *(positive pregnancy test on the day of randomization):*

( ) Yes (1)* → Elig ( ) No (2)

**Go to item 44.*

41. Is the patient currently breast feeding

( ) Yes (1)* → Elig ( ) No (2)

**Go to item 44.*

42. Per the Study Physician's judgment, is there any reason to exclude the patient from randomization:

( ) Yes (1)* → Elig ( ) No (2)

**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):*

( ) Yes (1)* ( ) No (2)†

45. → Elig

**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.

H. 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 8-43: (1)

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: (1)

h. INR > 1.3: (1)

i. Bilirubin > 2 mg/dL: (1)

j. Positive for hepatitis B: (1)

k. Positive for hepatitis C: (1)

l. ALT > 300 U/L: (1)

m. Fasting blood glucose ≥ 126 mg/dL: (1)

n. Creatinine > 2.0 mg/dL: (1)

o. Known intolerance to TZDs: (1)

p. Known intolerance to vitamin E: (1)

q. Liver transplant: (1)

r. Currently being evaluated for bariatric surgery: (1)

s. TPN in year prior to screening: (1)

t. Tests are outside time window and clinic chose not to repeat tests: (1)

u. Other reason not covered on this form *(specify):* (1)

_____
specify

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.)

PIVENS

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 Elig is checked for any item, the patient is not eligible for PIVENS and the form should not be keyed. If C 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of reading:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: h f 2

7. Study: PIVENS_2

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)

b. Masson's trichrome: (1)

C. NASH evaluation (use H & E and Masson's trichrome slides only)

10. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5% Elig (0)

5-33% (1)

34-66% (2)

> 66% (3)

b. Location:

Zone 3 (0)

Zone 1 (1)

Azonal (2)

Panacinar (3)

11. Fibrosis stage *(Masson's trichrome stain)*

0: None (0)

1a: Zone 3, perisinusoidal (requires trichome) (1)

1b: Zone 3, perisinusoidal (easily seen on H & E) (2)

1c: Portal/periportal only (3)

2: Zone 3 and periportal, any combination (4)

3: Bridging (5)

4: Cirrhosis (6)

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)

> 4 / 20x mag (3)

b. Amount of portal, chronic inflammation:

None to minimal (0)

Greater than minimal (1)

13. Hepatocellular ballooning:

None (0)

Few (1)

Many (2)

14. Is steatohepatitis present:

No (1)

Suspicious/borderline/indeterminate (2)

Yes, definite (3)

D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:

Yes (* 1) No (2)

C

** Caution: Primary biliary cirrhosis is exclusionary*

16. Is there evidence of Wilson's disease:

Yes (* 1) No (2)

C

** Caution: Wilson's disease is exclusionary*

17. Features of chronic cholestatic liver disease *(check all that apply)*

a. Bile duct loss/infiltration/sclerosis: (* 1)

C

b. Florid duct lesions: (1)

c. Cholate stasis: (1)

d. Copper deposition: (1)

e. Other *(specify):* (1)

_____

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: (1)

b. Inflammation suggestive of AIH, HCV: (* 1)

C

** Caution: Autoimmune liver disease and HCV are exclusionary*

c. Pigment suggestive of HH: (* 1)

C

** Caution: Hemochromatosis or iron overload as defined by 3+ or 4+ stainable iron is exclusionary*

d. Globules suggestive of A1AT: (* 1)

C

** Caution: Alpha-1 antitrypsin deficiency is exclusionary*

e. Hepatocellular changes suggestive of HBV: (* 1)

C

** Caution: HBV is exclusionary*

f. Granulomas suggestive of sarcoid, PBC, infection: (* 1)

C

** Caution: Primary biliary cirrhosis is exclusionary*

g. Other *(specify):* (1)

_____

h. None: (1)

19. Is there evidence of cirrhosis:

Yes (1) No (2)

E. NASH Activity Score

20. NASH activity score (NAS)
(sum of items 10a, 12a, and 13) ____ 3-8

(Note: each subscore must be 1 or more)

21. Is item 20 (NAS) 3 or less: Yes (1) 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:

_____

28. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: h i 1

7. Study: PIVENS 2

B. Interval identification

8. Date of last Followup Medical History form *(if this is visit f004 then date of s1):*

____ ____ – ____ ____ ____ – ____ ____
day mon year

9. Visit code of last Followup Medical History form *(if this is visit f004 then s1):*

____ ____ ____ ____

C. NASH evaluation

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

(Yes * 1) (No 2)

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

D. Alcohol consumption (AUDIT-C) since the last visit *(interview with patient)*

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

Never	(0)
	14.
Monthly or less	(1)
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 did you have 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)

13. 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. Tobacco cigarette smoking *(interview with patient)*

14. Since the last visit, have you smoked tobacco cigarettes regularly *("No" means less than 1 day per week on average):*

( ) Yes (1) ( ) No (2) → **17.**

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)*

a. Diabetes type 1: (1)

b. Diabetes type 2: (1)

c. Gestational diabetes *(diabetes of pregnancy):* (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)

l. 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)

r. Edema: (1)

s. Hepatic encephalopathy: (1)

t. Portal hypertension: (1)

u. Hepatorenal syndrome: (1)

v. Hepatopulmonary syndrome: (1)

w. Short bowel syndrome: (1)

x. Hemophilia *(bleeding disorder):* (1)

y. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

z. Endocrine disease *(hormonal abnormality):* (1)

aa. Hepatocellular carcinoma: (1)

ab. Other malignancy *(cancer):* (1)

ac. Human immunodeficiency virus (HIV): (1)

ad. Peripheral neuropathy: (1)

ae. Seizure disorder or epilepsy: (1)

af. Drug allergies: (1)

ag. Hypothyroidism: (1)

ah. Hypertension: (1)

ai. Cerebrovascular disease: (1)

aj. Dysbetalipoproteinemia: (1)

ak. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

al. Pancreatitis: (1)

am. Cholelithiasis: (1)

an. Coronary artery disease: (1)

ao. Congestive heart failure: (1)

ap. Elevated uric acid such as gout: (1)

aq. Kidney disease: (1)

ar. Polycystic ovary syndrome: (1)

as. Sleep apnea *(not breathing during sleep):* (1)

at. Dermatologic disorders: (1)

au. Myopathy: (1)

av. Myositis: (1)

aw. Major depression: (1)

ax. Schizophrenia: (1)

ay. Bipolar disorder: (1)

az. Obsessive compulsive disorder: (1)

ba. Severe anxiety or personality disorder: (1)

bb. Substance abuse: (1)

bc. None of the above: (1)

18. Since the last visit, has the patient had bariatric surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1)

b. Jejunoileal *(or other intestinal)* bypass: (1)

c. Biliopancreatic diversion: (1)

d. Other GI or bariatric surgery, *(specify):* (1)

_____

e. None of the above: (1)

19. Since the last visit, has the patient received an organ, limb, or bone marrow transplant:

Yes (1) No (2)

20. Since the last visit, has the patient received total parenteral nutrition (TPN):

Yes (1) No (2)

21. Since the last visit, has the patient been hospitalized *(complete an Interim Event Report (IE) form if possibly or definitely associated with PIVENS study drugs and this event has not already been reported on an IE form) :*

Yes (1) No (2)

22. ____

If Yes, specify reason:

_____

specify

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 (1) No (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): (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): (1)
i. Miglitol (Glycet): (1)
j. Nateglinide (Starlix): (1)
k. Pioglitazone (Actos) *(do not include PIVENS study medication):* (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: (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)
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)

_____

h. 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)
b. Colestipol hydrochloride (Colestid): (1)
c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)
d. Gemfibrozil (Gen-Fibro, Lopid): (1)
e. Fenofibrate (Tricor): (1)
f. Fluvastatin sodium (Lescol): (1)
g. Lovastatin (Mevacor): (1)
h. Nicotinic acid (Niaspan): (1)
i. Pravastatin sodium (Pravachol): (1)
j. Rosuvastatin (Crestor): (1)
k. Simvastatin (Zocor): (1)
l. Other, *(specify):* (1)

_____

m. None of the above: (1)

26. Since the last visit, has the patient taken any antiobesity medications *(check all that apply):*

a. Dexfenfluramine hydrochloride (Redux): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

c. Methamphetamine hydrochloride (Desoxyn, Gradumet): (1)

d. Orlistat (Xenical): (1)

e. Phendimetrazine tartrate (Adipost, Bontril): (1)

f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): (1)

g. Sibutramine hydrochloride monohydrate (Meridia): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

27. Since the last visit, has the patient taken any antitumor necrosis factor (anti-TNF) therapies *(check all that apply)*

a. Etanercept (Enbrel): (1)

b. Infliximab (Remicade): (1)

c. Other, *(specify):* (1)

_____
specify

d. None of the above: (1)

28. Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications *(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. Valdecoxib (Bextra): (1)

i. Other, *(specify):* (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 strong opiate medications containing acetaminophen *(check all that apply)*

a. Darvocet: (1)

b. Esgic - Plus: (1)

c. Fioricet: (1)

d. Lorcet: (1)

e. Lortab: (1)

f. Norco: (1)

g. Percocet: (1)

h. Talacen: (1)

i. Tylenol #3: (1)

j. Tylenol #4: (1)

k. Tylox: (1)

l. Vicodin: ( )

m. Wygesic: (1)

n. Other, *(specify):* (1)

_____

o. None of the above ( )

30. Since the last visit, has the patient taken any histamine H2 receptor antagonists or 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): (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)

31. Since the last visit, has the patient taken any anticoagulant or 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)

32. 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)

33. Since the last visit, has the patient taken any cardiovascular or antihypertensive medications *(check all that apply):*

a. Amiodarone (Pacerone): (1)
b. Amlodipine besylate (Norvasc): (1)
c. Atenolol (Tenormin): (1)
d. Benazepril (Lotensin): (1)
e. Captopril (Capoten): (1)
f. Clonidine (Catapres): (1)
g. Digoxin (Lanoxin): (1)
h. Diltiazem (Cardizem): (1)
i. Doxazosin (Cardura): (1)
j. Enalapril (Vasotec): (1)
k. Felodipine (Plendil): (1)
l. Furosemide (Lasix): (1)
m. Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)
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): (1)
s. Nifedipine (Adalat, Procardia): (1)
t. Perhexiline maleate: (1)
u. Propranolol (Inderal): (1)
v. Quinapril (Accupril): (1)
w. Terazosin (Hytrin): (1)
x. Timolol maleate (Blocadren): (1)
y. Valsartan (Diovan): (1)
z. Verapamil (Calan): (1)
aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

ac. 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 receptor modulators *(check all that apply):*

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

_____

u. Other, *(specify):* (1)

_____

v. None of the above: (1)

35. 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): (1)

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

g. Triamcinolone acetonide (Azmacort, Nasacort): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

36. Since the last visit, has the patient taken a multivitamin regularly:

Yes (1) No (2)

37. Since the last visit, has the patient taken vitamins other than multivitamins *(do not include PIVENS study medication):*

Yes (1) No (2)

40.

38. Which vitamins has the patient taken *(check all that apply):*

a. Vitamin B (any type): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Vitamin E (alpha-tocopherol): (1)

e. Other, *(specify):* (1)

_____

39. Is the patient currently taking vitamin E at a dose greater than 100 IU/day *(do not include PIVENS study medication):*

Yes (*1) No (2)

**Remind patient not to take vitamin E supplements at doses greater than 100 IU/day during PIVENS.*

40. Since the last visit, has the patient taken any supplements *(check all that apply):*

a. Alpha-lipoic acid: (1)

b. Beta-carotene: (1)

c. Betaine (Cystadane): (1)

d. Calcium (any form): (1)

e. Carnitine (any form): (1)

f. Chondroitin (any form): (1)

g. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)

h. Cod liver oil: (1)

i. Coenzyme Q: (1)

j. Dichloroacetate: (1)

k. Echinacea: (1)

l. Fish oil (any form): (1)

m. Flax seed oil: (1)

n. Garlic: (1)

o. Ginkgo biloba: (1)

p. Glucosamine (any form): (1)

q. Lecithin: (1)

r. Magnesium: (1)

s. Milk thistle: (1)

t. N-acetyl-cysteine: (1)

u. Potassium (any form): (1)

v. Probiotics (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)

_____

ad. Other, *(specify):* (1)

_____

ae. None of the above: (1)

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): (1)

b. Divalproex (Depakote): (1)

c. Doxycycline (Monodox): (1)

d. Isotretinoin (Accutane): (1)

e. Levothyroxine (Levoxyl, Synthroid): (1)

f. Liothyronine (Cytomel): (1)

g. Methotrexate (Rheumatrex): (1)

h. Minocycline (Dynacin, Minocin): (1)

i. Oxytetracycline (Terramycin): (1)

j. Penicillamine (Cuprimine, Depen): (1)

k. Tetracycline (Achromycin): (1)

l. Trientine hydrochloride (Syprine): (1)

m. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)

n. Valproate sodium (Depacon): (1)

o. Valproic acid (Depakene): (1)

p. Other, *(specify):* (1)

_____

q. Other, *(specify):* (1)

_____

r. Other, *(specify):* (1)

_____

s. Other, *(specify):* (1)

_____

t. Other, *(specify):* (1)

_____

u. None of the above: (1)

H. Administrative information

42. Study Physician PIN: ____ ____ ____

43. Study Physician signature:

_____

44. Clinical Coordinator PIN: ____ ____ ____

45. Clinical Coordinator signature:

_____

46. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: h s 1

7. Study PIVENS 2

B. 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

C. Administrative information

10. Clinical Coordinator PIN: ____ ____ ____

11. Clinical Coordinator signature:

_____

12. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: h t 1

7. Study: PIVENS 2

B. Steatohepatitis determination

8. Is steatohepatitis present:

No (1)
Suspicious/borderline/indeterminate (2)
Yes, definite (3)

9. 2nd Pathologist

a. 2nd Pathologist PIN *(use initials if no PIN is available):*

____ ____ ____

b. 2nd Pathologist signature:

_____

c. Date of slide reading:

____ ____–____ ____ ____–____ ____
day mon year

C. Administrative information

10. Clinical Coordinator PIN: ____ ____ ____

11. Clinical Coordinator signature:

_____

12. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: i e 1

7. Study: PIVENS 2

B. Visit interval identification

8. Most recently completed visit (screening or followup)

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____ ____

C. Patient information

9. Date randomized in PIVENS *(enter n if patient is not yet randomized):*

____ ____–____ ____ ____–____ ____
day mon year

10. Gender:

Male (1)
Female (2)

11. Age at time of event: ____ ____
years

12. Is the patient currently receiving the pioglitazone-series study drug:

Yes (1) No (2)

13. Is the patient currently receiving the vitamin E-series study drug:

Yes (1) No (2)

14. Summarize the patient's history of treatment with PIVENS study drugs *(eg, how long has patient been on study drugs, have there been any treatment interruptions):*

D. Event description

15. Is the event associated with PIVENS study drugs:

(Yes 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:

____ ____–____ ____ ____–____ ____
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: (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. 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)

_____

_____

22. Severity grade *(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 Serious Adverse Event Report (AN) to report serious and unexpected adverse events of call the DCC if unsure what to do:*

Not applicable	(0)
Grade 1 - Mild	(1)
Grade 2 - Moderate	(2)
Grade 3 - Severe	(3)
Grade 4 - Life threatening or disabling	(4)
Grade 5 - Death	(*5)

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

23. Date event resolved *(enter n if event is not yet resolved):*

____ ____–____ ____ ____–____ ____
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:

____ ____–____ ____ ____–____ ____
day mon year

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.

PIVENS

LD – Lifetime Drinking History (Skinner)

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 patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: **s** **2** _____ _____

6. Form & revision: **l** **d** **1**

7. Study: PIVENS 2

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):

Yes (1) No (2)

81. ◄

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)*	(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)*:

	Positive	Negative	Neutral
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)

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 ____ ____ % ____

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":

Yes (1) No (2)

81. ↵

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:

Yes (1) No (2)

30. ↵

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)*:

		Positive	Negative	Neutral
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)

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 ____ ____ ____ %

With others ____ ____ ____ %

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 be "000")*:

Morning ____ ____ ____ %

Afternoon ____ ____ ____ %

Evening ____ ____ ____ %

E. Next 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 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 (1) No (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:

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")*:

Beer ____ ____ ____ %

Liquor ____ ____ ____ %

Wine ____ ____ ____ %

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)

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

Yes (1) No (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)*:

	Positive	Negative	Neutral
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":

Yes (1) No (2)

→ **81.**

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

a. Years: ____ ____ yrs

b. Months: ____ ____ mos

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:

____ ____ # drinks

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

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 (1) No (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)*:

		Positive	Negative	Neutral
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"*:

Yes (1) No (2)

81. ↵

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

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

____ ____
drinks

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

____ ____
days

61. 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.*)

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 ____ ____ ____
%

Liquor ____ ____ ____
%

Wine ____ ____ ____
%

63. 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)

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

Yes (1) No (2)

66. ◄

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 effect)*:

	Positive	Negative	Neutral
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)

66. 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 ____ ____ ____
%

67. 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 ____ ____ ____
%

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 (1) No (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.*)

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 ____ ____ % ____

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)

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

Yes (1) No (2)

78. ↵

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)*:

	Positive	Negative	Neutral
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)

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 ____ ____ ____ %

Evening ____ ____ ____ %

I. Number of phases

80. Are there any additional subsequent phases:

Yes (* 1) No (1)

***** *If yes, complete a second LD form.*
Skip sections B and C on second form.

J. Administrative information

81. Clinical Coordinator PIN: ____ ____ ____

82. Clinical Coordinator signature:

_____

83. Date form reviewed:

____ ____-____ ____ ____-____ ____
day mon 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. 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: **l q 1**

7. Study: PIVENS 2

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. Clinical Coordinator
- **a**. PIN: _____ _____ _____
- **b**. Signature: _____

9. 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 (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
l. 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

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 3
I have fatigue and it keeps me from doing what I want to do 4
I have fatigue that prevents me from working 5
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 2
At least part of several days a week 3
At least part of one day a week 4
Less frequently 5

13. Is your fatigue typically present *(choose only one)*:

When you wake up in the morning 1
Or does it come on with the day 2
Or does it have no time pattern 3

14. Is your fatigue typically worse the day after a period of extra activity or exercise:

Yes 1
No 2

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):

Circle one

Yes 1
No 2

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

Very good 1
Good 2
Fair 3
Poor 4
Awful 5

17. Today's date:

_____

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 (Ineligible) 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: 1 r 1

7. Study: PIVENS 2

B. Hematology

Required at visits s1, f024, f048, f096, and f120.

8. Is hematology testing required at this visit:

( ) Yes (1) ( ) No (2)
14.

9. Date of blood draw for complete blood count:

____ ____–____ ____ ____–____ ____
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).

10. Hemoglobin: ____ ____ • ____ ____ g/dL

11. Hematocrit: ____ ____ • ____ ____ %

12. White blood cell count (WBC):

____ ____ • ____ ____
10^3 cells/ µL or 10^9 cells/L

13. Platelet count:

____ ____ ____, ____ ____ ____
cells/ µL

C. Chemistries

Required at visits s1, f024, f048, and f096.

14. Is metabolic panel required at this visit:

( ) Yes (1) ( ) No (2)
27.

15. Date of blood draw for chemistries:

____ ____–____ ____ ____–____ ____
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).

16. Sodium: ____ ____ ____ mEq/L

17. Potassium: ____ ____ • ____ ____ mEq/L

18. Chloride: ____ ____ ____ mEq/L

19. Bicarbonate: ____ ____ • ____ ____ mEq/L

20. Calcium: ____ ____ • ____ ____ mg/dL

21. Phosphate: ____ ____ • ____ ____ mg/dL

22. Blood urea nitrogen (BUN): ____ ____ mg/dL

23. Creatinine *(if serum creatinine ≥ 2.0 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:

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

33.

28. Date of blood draw for prothrombin time, GGT, and HbA1c:

____ ____–____ ____ ____–____ ____
day mon year

Date must be in the time window for the followup visit (check the patient's PIVENS visit time window guide).

29. Prothrombin time (PT): ____ ____ • ____
sec

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:

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

40.

34. Date of blood draw for liver panel:

____ ____–____ ____ ____–____ ____
day mon year

Date must be in the time window for the followup visit (check the patient's PIVENS visit time window guide).

35. Bilirubin (total): ____ ____ • ____
mg/dL

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)

____ ____ ____
U/L

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 s1, 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:

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

42.

41. 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 PIVENS visit time window guide).

a. Triglycerides: ____ ____ ____ mg/dL

b. Total cholesterol: ____ ____ ____ mg/dL

c. HDL cholesterol level: ____ ____ ____ mg/dL

d. LDL cholesterol level: ____ ____ ____ mg/dL

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:

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

45.

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)

52.

No, patient is diabetic ( ) (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: ____ ____ ____ • ____ μU/mL

c. Serum C peptide: ____ ____ • ____ ng/mL

48. OGTT results at 30 minutes

a. Serum glucose: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ μU/mL

49. OGTT results at 1 hour

a. Serum glucose: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____ µU/mL

50. OGTT results at 90 minutes

a. Serum glucose: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____ µU/mL

51. OGTT results at 2 hours

a. Serum glucose: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____ µU/mL

I. Microalbuminuria

Required at visits f048, f096, and f120.

52. Is microalbuminuria required at this visit:

Yes (1) No (2)

55.

53. Date of urine collection for dipstick:

____ ____–____ ____ ____–____ ____
day mon year

Date must be in the time window for the followup visit (check the patient's PIVENS visit time window guide).

54. Microalbuminuria:

Positive (1)
Negative (2)

J. Pregnancy test

Required at all study visits if applicable.

55. Is pregnancy test applicable:

Yes (1) No (2)

58.

56. Date of urine collection (or blood draw):

____ ____–____ ____ ____–____ ____
day mon year

Date must be the same day as date of visit.

57. Pregnancy test result *(if pregnancy test is positive at s1, patient is ineligible):*

Positive (1)
Negative (2)

K. Eligibility check

58. Is this the s1 visit:

Yes (1) No (2)

60.

59. Was the patient found to be ineligible based on creatinine (item 23), albumin (item 25), serum glucose (item 44), or pregnancy test (item 57):

Yes (1) No (2)

Elig

L. Administrative information

60. Study Physician PIN: ____ ____ ____

61. Study Physician signature:

_____

62. Clinical Coordinator PIN: ____ ____ ____

63. Clinical Coordinator signature:

_____

64. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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 EHg 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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: 1 s 1

7. Study: PIVENS 2

B. Screening etiologic tests

8. Date of blood draw for serological assays to exclude viral causes of chronic liver disease:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 1 year prior to screening.

a. Hepatitis B surface antigen (HBsAg):
Positive (1) EHg ____
Negative (2)

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 (1)
Negative (2)
Not available (3)

d. Hepatitis C antibody (anti-HCV) *(indicate result as negative if EIA is positive but RIBA is negative):*
Positive (1) EHg ____
Negative (2)

e. Hepatitis C virus RNA (HCV RNA):
Positive (1) EHg ____
Negative (2)
Not available (3)

C. Autoantibody studies

9. Date of blood draw for autoantibody studies:

___ ___–___ ___ ___–___ ___
day mon year

Repeat if date is greater than 5 years prior to screening.

10. Antinuclear antibody (ANA):

Positive (* 1)
Negative (2)
12.

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

Yes (* 1) No (2)
C

** Check Liver Biopsy Histology Findings Form for autoimmune liver disease.*

12. Antimitochondrial antibody (AMA):

Positive (* 1)
Negative (2)
14.

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

Yes (* 1) No (2)
C

** Check Liver Biopsy Histology Findings Form for primary biliary cirrhosis.*

14. Antismooth muscle antibody (ASMA):

Positive (* 1)
Negative (2)
15.

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:

Yes (1) No (2)
18.

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

a. Lower limit of normal: ___ ___ • ___ mg/dL

b. Is ceruloplasmin below the lower limit of normal:

Yes (* 1) No (2)
C

** Check Liver Biopsy Histology Findings Form for Wilson's Disease.*

E. Alpha-1 antitrypsin

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

___ ___–___ ___ ___–___ ___
day mon year

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

19. Alpha-1 antitrypsin (A1AT)

___ ___ ___ mg/dL

a. Lower limit of normal: ___ ___ ___ mg/dL

b. Is A1AT below the lower limit of normal:

Yes (* 1) No (2)
C

** 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.

a. Iron: ____ ____ ____ µg/dL

b. Total Iron Binding Capacity: ____ ____ ____ µg/dL

c. Ferritin: ____ ____ ____ ____ ng/mL

21. Is hepoatic iron index available:

Yes (1) No (2)

23.

22. Hepatic iron index: ____ • ____ µmol/g/year

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code *(s1 or f096):* ____ ____ ____ ____

6. Form & revision: 1 t 1

7. Study: PIVENS 2

B. Liver biopsy

8. Date of biopsy:

____ ____–____ ____ ____–____ ____
day mon year

9. Was the liver tissue obtained using a 16-gauge or greater needle:

Yes (1) No (2)

10. Was liver tissue obtained via a second pass:

Yes (1) No (2)

11. Was the liver tissue obtained from a needle core biopsy *(as opposed to a wedge biopsy):*

Yes (1) No (2)

C. Cryovial label

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):*

D. Flash freeze procedures

13. Was tissue flash frozen within 5 minutes of biopsy by placing in portable liquid nitrogen container:

Yes (1) No (2)

15. ____

14. Explain what was done and why protocol was not followed:

_____

_____

_____

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

Yes (1) No (2)

17. ____

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

PIVENS

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 EHG 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 2 ____ ____

6. Form & revision: l u 1

7. Study: PIVENS 2

B. Prothrombin time, GGT, and HbA1c

8. Date of blood draw for prothrombin time, GGT, and HbA1c:

____ ____–____ ____ ____–____ ____
day mon year
Date must be within 3 months of screening.

9. Prothrombin time (PT): ____ ____ • ____
sec

10. International normalized ratio (INR) *(if INR > 1.3 and physician judges patient has cirrhosis, patient is ineligible):*

____ • ____

11. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

12. HbA1c: ____ ____ • ____
%

C. Liver panel

13. Date of blood draw for liver panel:

____ ____–____ ____ ____–____ ____
day mon year
Date must be within within 3 months of screening.

14. Bilirubin (total): ____ ____ • ____
mg/dL

15. Bilirubin (conjugated or direct) *(if conjugated bilirubin > 2 mg/dL and physician judges patient has cirrhosis, patient is ineligible):*

____ • ____
mg/dL

16. Aspartate aminotransferase (AST)

____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

b. Lower limit of normal: ____ ____ ____
U/L

17. Alanine aminotransferase (ALT) *(if ALT > 300 U/L, patient is ineligible)*

____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

b. Lower limit of normal: ____ ____ ____
U/L

18. Alkaline phosphatase ____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

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 blood draw for OGTT:

____ ____–____ ____ ____–____ ____
day mon year

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):*

____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____
µU/mL

c. Serum C peptide: ____ ____ • ____ ____
ng/mL

21. OGTT results at 30 minutes

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____
µU/mL

22. OGTT results at 1 hour

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____
µU/mL

23. OGTT results at 90 minutes

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____
µU/mL

24. OGTT results at 2 hours

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____ ____
µU/mL

E. Microalbuminuria

25. Date of urine collection for dipstick:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within 3 months of screening.

26. Microalbuminuria:

Positive (1)
Negative (2)

F. Pregnancy test

27. Is pregnancy test applicable:

Yes (1) No (2)
30.

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):

Yes (1) No (2)
Elig

H. 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

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed: ____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: f ____ ____ ____

6. Form & revision: m v 2

7. Study: PIVENS 2

B. Reason for completion of this form

8. Was the entire visit missed:
Yes (1) No (2)
11.

C. Missed visit information

9. Reason for missed visit *(check all that apply)*

a. Patient was ill: (1)
b. Patient was temporarily away from area: (1)
c. Patient refused to return: (1)
d. Patient has permanently moved from the area: (1)
e. Unable to contact patient: (1)
f. Other *(specify):* (1)

_____
specify

10. Steps taken to avoid missing the visit *(check all that apply)*

a. Telephoned patient: (1)
b. Mailed reminder card: (1)
c. Other *(specify):* (1)

_____
specify

14.

D. Missed form information

11. Check form(s) not completed *(check all that apply)*

a. Food Questionnaire Documentation (BD): (1)
b. Blood Processing for Plasma and Serum (BP): (1)
c. DEXA Scan for Bone Mineral Density (DD): (1)
d. DEXA Scan for Body Fat (DX): (1)
e. Followup Medical History (HI): (1)
f. Symptoms of Liver Disease (LQ): (1)
g. Laboratory Results - Tests Done During Screening and Followup (LR): (1)
h. Liver Tissue Banking (LT): (1)
i. Physical Activity (PA): (1)
j. Physical Examination (PE): (1)
k. Focused Physical Examination (PF): (1)
l. MOS 36-Item Short-form Health Survey (QF): (1)
m. Study Drug Dispensing and Return (RD): (1)
n. Liver Biopsy Materials Documentation (SD): (1)
o. 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. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

PA – Physical Activity

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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p a 1**

7. Study: PIVENS 2

B. Administrative information
(To be completed by Clinical Coordinator after survey is completed.)

8. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature: _____

9. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

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.

Circle one

10. Level of activity that best describes your usual non-recreational activity.

Vigorous or strenuous activity: 1
(involves heavy lifting, digging, handling heavy tools or equipment, or any other activity causing you to work up a sweat or get out of breath)

Moderate activity: 2
(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: 3
(involves sitting down with one hand movement, moderate one-arm work or light two-arm work, with occasional walking or standing such as office work, filing or sorting, or light or moderate housework)

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

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	Hours: _____ _____ 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: _____ _____

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: _____ _____
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 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 measuerments 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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: p e 1

7. Study: PIVENS 2

B. Measurements

8. Height *(shoes off)*

a. 1st measurement: ____ ____ ____ • ____

b. 2nd measurement: ____ ____ ____ • ____

c. Units:
Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement: ____ ____ ____ • ____

b. Weight, 2nd measurement: ____ ____ ____ • ____

c. Units:
Pounds (1)
Kilograms (2)

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)*

a. Circumference, 1st measurement: ____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement: ____ ____ ____ • ____
waist circumference

c. Units:
Inches (1)
Centimeters (2)

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)*

a. Circumference, 1st measurement:

___ ___ ___ • ___
hip circumference

b. Circumference, 2nd measurement:

___ ___ ___ • ___
hip circumference

c. Units:

Inches (1)
Centimeters (2)

12. Triceps *(right arm, with elbow extended and arm relaxed; repeat skin fold measurements until you have two within 10 mm of each other; repeat mid-upper arm circumference until you have two within 1.5 in (3.8 cm) of each other)*

a. Skin fold, 1st measurement:

___ ___ ___ • ___
mm

b. Skin fold, 2nd measurement:

___ ___ ___ • ___
mm

c. Mid-upper arm circumference, 1st measurement:

___ ___ • ___
arm circumference

d. Mid-upper arm circumference, 2nd measurement:

___ ___ • ___
arm circumference

e. Units for arm circumference:

Inches (1)
Centimeters (2)

13. Temperature *(oral)*

a. Degrees: ___ ___ ___ • ___

b. Scale:

Fahrenheit (1)
Centigrade (2)

14. Blood pressure

a. Systolic: ___ ___ ___
mmHg

b. Diastolic: ___ ___ ___
mmHg

15. Resting radial pulse: ___ ___ ___
beats/minute

16. Respiratory rate: ___ ___
breaths/minute

C. Examination findings

17. Skin:

Normal (1)
20. ⌐
Abnormal (2)

18. Acanthosis nigricans *(check only one):*

Absent *(not detectable on close inspection)* (0)

Present *(clearly present on close inspection, not visible to casual observer, extent not measurable)* (1)

Mild *(limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth)* (2)

Moderate *(extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front)* (3)

Severe *(extending anteriorly, > 6 inches in breadth, visible from front)* (4)

19. Other skin abnormality *(check all that apply)*

a. Jaundice: (1)
b. Palmar erythema: (1)
c. Spider angiomata: (1)
d. Other *(specify):* (1)

_____

e. None of the above: (1)

20. Head, eyes, ears, nose, throat:

Normal (1)
22. ⌐
Abnormality (2)

21. Abnormality of the head, eyes, nose, throat
(check all that apply)

a. Jaundice: (1)
b. Other *(specify):* (1)

_____
specify

22. Neck:

Normal (1)

Abnormal (2)

23.

_____
specify abnormality

23. Lymphatic:

Normal (1)

Abnormal (2)

24.

_____
specify abnormality

24. Chest and lungs:

Normal (1)

Abnormal (2)

25.

_____
specify adnormality

25. Heart:

Normal (1)

Abnormal (2)

26.

_____
specify abnormality

26. Abdomen:

Normal (1)

Abnormal (2)

28.

27. Abdomen abnormality
(check all that apply)

a. Ascites: (1)

b. Obese: (1)

c. Other *(specify):* (1)

_____
specify abnormality

28. Liver and spleen:

Normal (1)

Abnormal (2)

30.

29. Abnormality of liver or spleen *(check all that apply)*

a. Hepatomegaly: (1)
(if checked, span from right midclavicular line):

___ ___ • ___
cm

b. Splenomegaly: (1)

c. Other *(specify):* (1)

_____
specify abnormality

30. Extremities:

Not performed (0)

32.

Normal (1)

32.

Abnormal (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)

e. Other *(specify):* (1)

_____
specify abnormality

32. Genitourinary/pelvis:

Not performed (0)

33.

Normal (1)

33.

Abnormal (2)

_____
specify abnormality

33. Nervous system:

Not performed (0)

35.

Normal (1)

35.

Abnormal (2)

34. Abnormality of the nervous system
(check all that apply)

a. Mental status abnormal: (1)

b. Asterixis: (1)

c. Other *(specify):* (1)

_____
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

PIVENS

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: p f 1

7. Study: PIVENS 2

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

10. Waist *(standing, at midpoint between highest point of iliac crest and lowest part of costal margin; repeat waist measurements until you have two within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

11. Hip *(standing, at fullest part of the hips; repeat hip measurements until you have two within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:
Fahrenheit: (1)
Centigrade: (2)

13. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

14. Resting radial pulse: ____ ____ ____ beats/minute

15. Respiratory rate: ____ ____ breaths/minute

C. Liver signs

16. Liver and spleen:

Normal (1)

18.

Abnormal (2)

17. Abnormality *(check all that apply)*

a. Ascites: (1)

b. Asterixis: (1)

c. Contractures: (1)

d. Hepatomegaly: (1)

If Yes, span from right midclavicular line:

____ ____ • ____ cm

e. Jaundice: (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

D. Administrative information

18. Study Physician ID: ____ ____ ____

19. Study Physician signature:

_____

20. Clinical Coordinator ID: ____ ____ ____

21. Clinical Coordinator signature:

_____

22. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

PIVENS

QF – MOS 36-Item Short-Form Health Survey

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.

A. Center, visit, and patient identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **q f 1**

7. Study: PIVENS 2

B. Administrative information
(To be completed by Clinical Coordinator after survey is completed.)

8. Clinical Coordinator PIN: _____ _____ _____

9. Clinical Coordinator signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

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:

	Circle One
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

12. Compared to one year ago, how would you rate your health in general now?

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

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?

Activities	**Circle one**		
	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 label here

Patient ID: __ __ __ __

Pt 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 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

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?

Circle One

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

17. How much bodily pain have you had during the past 4 weeks?

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

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 1

A little bit 2

Moderately 3

Quite a bit 4

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.)?

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: __ __ __ __

Pt code: __ __ __

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:

_____

Please bring this completed survey with you to your scheduled PIVENS study visit.

PIVENS

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: r c 1

7. Study: PIVENS_2

B. PIVENS participation

8. Date in item 4 of original PIVENS RG form: ____ ____–____ ____ ____–____ ____
day mon year

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature: _____

11. Date form reviewed: ____ ____–____ ____ ____–____ ____
day mon year

PIVENS

RD – Study Drug Dispensing and Return

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:

Visit	*No. of P series bottles*	*No. of E series 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **r d 2**

7. Study: PIVENS 2

B. Study drug dispensing

8. Is this a second form for returning additional drug bottles at this visit: Yes (1) No (2)

→ **18.**

9. Will study drug be dispensed today: Yes (1) No (2)

→ **11.**

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: (1)
- **d.** Other *(specify)*: (1)

_____
specify

→ **18.**

11. Number of P series bottles issued: _____ (1-2)

Bottle tear-off label

12.

Affix label here

13.

Affix label here

14. Number of E series bottles issued: _____ (1-2)

Bottle tear-off label

15.

Affix label here

16.

Affix label here

17. How were the study drugs dispensed to the patient *(check only one)* :

In person	(1)
Mail	(2)
Other *(specify)*	(3)

_____
specify

C. Study drug return

18. Were any P series bottles returned at this visit:

Yes (1) No (2)

26. ◄

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:

Yes (1) No (2)

34. ◄

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.	E ___ ___ ___ ___	___ ___ (00-50)
33.	E ___ ___ ___ ___	___ ___ (00-50)

D. Remaining bottles

34. Are any additional bottles being returned:

Yes (* 1) No (2)

**If yes, complete a second RD form using visit code "n."*

E. Administrative information

35. Clinical Coordinator 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 assigned an ID for a NASH CRN study.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: r g 1

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:

Yes (1) No (2)

STOP

9. Has the patient signed the PIVENS informed consent statement:

Yes (1) No (2)

STOP

10. Has the consenter or study physician signed the consent form:

Yes (1) No (2)

STOP

C. Information about patient

11. Date of birth:

____ ____–____ ____ ____–____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

12. Age at last birthday: ____ ____ years

13. Gender:

Male (1)
Female (2)

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):*

Hispanic or Latino or Latina (1)
Not Hispanic, not Latino, not Latina (2)

16. ____

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 Card #2 and ask the patient to pick the category or categories that describes him/her best; check all that apply)*

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)

17. In what country was the patient born *(check only one)*:

Continental US (includes Alaska) or Hawaii (1)

Other, *(specify)*: (2)

_____
specify

18. Highest educational level achieved by patient *(show the patient Flash Card #3 and ask the patient to pick the category that describes him/her best; check only one)*:

Never attended school (0)

Kindergarten, pre kindergarten, or younger (1)

Grades 1 to 5 (2)

Grades 6-8 (3)

Grades 9-11 (4)

Completed high school (5)

Some college or post high school education or training (6)

Bachelor's degree or higher (7)

19. Is the patient currently employed:

Yes (1) No (2)

22. ____

20. What is the patient's current occupation:

_____
specify occupation

21. About how many hours does the patient work each week: ____ ____
hours

22. Which of the following categories best characterizes the patient's occupational history *(show patient Flash Card #4 and ask the patient to pick the category that describes him/her best; check only one)*:

Never employed (0)

Laborer (1)

Clerical (2)

Professional (3)

Homemaker (4)

Other, *(specify)*: (5)

_____
specify

23. Marital status of the patient *(show patient Flash Card #5 and ask the patient to pick the category that describes him/her best; check only one)*:

Single, never married (1)

Married or living in marriage-like relationship (2)

Separated, divorced, or annulled (3)

Widowed (4)

24. Combined annual income before taxes of all members of patient's household *(show patient Flash Card #6 and ask the patient to pick the category that describes his/her 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

(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	(08)
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:

Yes (1) No (2)

31.

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):*

____ ____ ____

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) **32.**
Yes	(1) **32.**
No	(* 2) **32.**

** 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, patient 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:

Yes (1) No (* 2)

STOP

** 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 (3)

C. Requirements for screening biopsy

10. Is this visit s1:

Yes (1) No (2)

13. ____

11. Is the date in item 9 within 6 months (183 days) of the anticipated date of randomization:

Yes (1) No (* 2)

Elig ____

** 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:

Yes (*1) No (+2)

Elig

** 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:

Yes (*1) 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: (1)

b. Masson's trichrome stain: (1)

c. Iron stain: (1)

E. Unstained slides to be sent to the DCC

15. Are unstained slides available for sending to the DCC:

Yes (1) No (2)

18.

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 number ___ ___ (01-60)

c. 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

Yes (1) No (2)

21.

19. Slide sequence number for this slide *(from the NASH CRN label on the slide - use removable overlabels, sequence numbers 81 - 90):*

___ ___ (81-90)

20. Is the H & E stained slide to be returned to the clinical center:

Yes (1) No (2)

21. Is the institution's Masson's trichrome stained slide to be sent to the DCC:

Yes (1) No (2)

24.

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:

(Yes 1) (No 2)

24. Is the institution's iron stained slide to be sent to the DCC:

(Yes 1) (No 2)

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:

(Yes 1) (No 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):*

(Yes 1) (No 2)

30.

28. 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)

29. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department (1)

30.

Other, *(specify):* (2)

_____
name

_____
address

_____
address

_____
address

_____
phone

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of notification of intent to transfer:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____

6. Form & revision: t n 1

7. Study: PIVENS 2

B. Last followup visit information

8. Date of last followup visit:

____ ____–____ ____ ____–____ ____
day mon year

9. Visit ID code of last completed followup visit: f ____ ____ ____

10. Have cryovial and slide labels been sent to the adopting center:

Yes (1) No (* 2)

** Send the cryovial and slide labels to the adopting center.*

C. Enrolling center administrative information

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

12. Clinical coordinator ID: ____ ____ ____

13. Clinical coordinator signature:

_____

D. Adopting center, patient and visit identification

14. Adopting center ID: ____ ____ ____ ____

15. Patient ID *(must be same as in Section A):*

____ ____ ____ ____

16. Patient code: *(must be same as in Section A):*

____ ____ ____

17. Expected date of first followup visit at adopting center:

____ ____–____ ____ ____–____ ____
day mon year

18. Visit ID code for expected first followup visit at adopting center: f ____ ____ ____

Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.

E. Adopting center administrative information

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

20. Clinical coordinator ID: ____ ____ ____

21. Clinical coordinator signature:

_____

Fax form to the DCC. The DCC will key the TN form.

NASH CRN TONIC

TONIC Form Abbreviations and Case Report Form Names

Form	Form Name
AD	AUDIT – Alcohol Use Disorders Identification Test
BC	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
IE	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

TN	Transfer Notification

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. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: **s 1** _____ _____

6. Form & revision: **a d 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient (1)
→ **10.**
Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that 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

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)

→ **22.**

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?

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

15. 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
(0)	(1)	(2)	(3)	(4)

16. 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
(0)	(1)	(2)	(3)	(4)

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?

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

18. 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
(0)	(1)	(2)	(3)	(4)

19. 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
(0)	(1)	(2)	(3)	(4)

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

No	Yes, but not in the last year	Yes, during the last year
(0)	(1)	(2)

21. 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
(0)	(1)	(2)

22. Today's date:

_____

Thank you for completing this questionnaire.

TONIC

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b c 1

7. Study: TONIC_3

B. Check on consent

8. Did the patient/parent consent/assent to blood draw for DNA extraction:

Yes (1) No (* 2)

STOP

** You cannot proceed until you get consent.*

9. Did the patient previously provide blood for DNA banking in the NAFLD Database:

Yes (1) No (2)

15.

C. Specimen for Genetics Repository

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 the NIDDK Genetics Repository.

10. Was blood collected for the NIDDK Genetics Repository:

Yes (1)

11.

No, *(specify):* (2)

_____
specify

15.

11. Date and time of blood draw

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour minute am pm

12. Number of 10 mL EDTA tubes: ____

13. Form copy of tube labels:

TONIC Form BC
Pt: ccc- 9999, xyz
Gender
Age, yrs.: XX

14. Phlebotomist:

_____
print name

D. Administrative information

15. Clinical Coordinator PIN: ____ ____ ____

16. Clinical Coordinator signature:

_____

17. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

TONIC

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed *(date food questionnaire booklet is completed):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b d 1

7. Study: TONIC 3

B. Administration of food questionnaire

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 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

10. Form copy of label applied to food questionnaire:

TONIC Form BD
Pt: 9999,xyz
Visit: vvvv
Date: _____

C. Administrative information

11. Clinical Coordinator PIN: ____ ____ ____

12. Clinical Coordinator signature:

_____

13. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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 ⚠C is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for TONIC. If EXC 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.

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: s 1 ____ ____

6. Form & revision: b g 2

7. Study: TONIC 3

B. Family history

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

Yes (1) No (2)
10.

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

a. Alcohol related liver disease: (1)
b. Viral hepatitis: (1)
c. Alpha-1 antitrypsin deficiency: (1)
d. Wilson's disease: (1)
e. Glycogen storage disease: (1)
f. Hemochromatosis or iron overload: (1)
g. Fatty liver disease *(NAFLD, NASH):* (1)
h. Primary liver cancer: (1)
i. Type of liver disease unknown: (1)
j. Other *(specify):* (1)

_____
specify

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

Yes (1) No (2)
12.

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

Yes (1) No (2)

12. Do any of the patient's first degree relatives (parent, brother, sister) 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) have obesity:

Yes (1)
No (2)
Don't know (3)

14. Do any of the patient's first degree relatives (parent, brother, sister) have atrophy of body fat:

Yes (1)
No (2)
Don't know (3)

15. Do any of the patient's first degree relatives (parent, brother, sister) have a problem with cholesterol or blood fat:

Yes (1)
No (2)
Don't know (3)

C. NAFLD history

16. Date patient was first diagnosed with nonalcoholic fatty liver disease (NAFLD):

____ ____–____ ____ ____–____ ____
day mon year

17. What prompted the evaluation for NAFLD *(check all that apply)*

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)
e. Other *(specify):* (1)

_____
specify

18. What procedures/tests supported this first diagnosis *(check all that apply)*

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

_____
specify

D. Weight history

19. What was the patient's birthweight:

____ ____–____ ____
lbs oz

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

E. Tobacco cigarette smoking history

(interview with patient; not by chart review)

23. Have you ever smoked tobacco cigarettes:

Never (1)
28.
In the past but not anymore (2)
Currently smokes cigarettes (3)

24. 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):*

Yes (1) No (2)
28.

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

____ ____
years

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

____ ____
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:

(Yes 1) (No 2)

31.

29. Menarche history

a. Has menarche occurred:

(Yes 1) (No 2)

31.

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 *(⚠C means 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: ⚠C (1)

b. Diabetes type 2: ⚠C (1)

c. Gestational diabetes *(diabetes of pregnancy):* (1)

d. Hepatitis B: ⚠C (1)

e. Hepatitis C: ⚠C (1)

f. Autoimmune hepatitis: ⚠C (1)

g. Autoimmune cholestatic liver disorder (PBC or PSC): ⚠C (1)

h. Wilson's disease: ⚠C (1)

i. Alpha-1-antitrypsin (A1AT) deficiency: ⚠C (1)

j. Hemochromatosis or iron overload: ⚠C (1)

k. Drug induced liver disease: ⚠C (1)

l. Gilbert's syndrome: (1)

m. Esophageal or gastric varices on endoscopy: ⚠C (1)

n. Bleeding from varices: ⚠C (1)

o. Other gastrointestinal bleeding: (1)

p. Biliary diversion: (1) C

q. Metabolic acidosis: (1) C

r. Ascites: (1) C

s. Edema: (1)

t. Hepatic encephalopathy: (1) C

u. Portal hypertension: (1) C

v. Hepatorenal syndrome: (1) C

w. Hepatopulmonary syndrome: (1) C

x. Short bowel syndrome: (1) C

y. Hemophilia *(bleeding disorder):* (1) C

z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

aa. Endocrine disease *(hormonal abnormality):* (1)

ab. Hepatocellular carcinoma: (1) C

ac. Other malignancy *(cancer):* (1) C

ad. Human immunodeficiency virus (HIV): (1) C

ae. Peripheral neuropathy: (1)

af. Seizure disorder or epilepsy: (1)

ag. Drug allergies: (1)

ah. Hypothyroidism: (1)

ai. Hypertension: (1)

aj. Cerebrovascular disease: (1)

ak. Dysbetalipoproteinemia: (1) C

al. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

am. Pancreatitis: (1)

an. Cholelithiasis: (1) C

ao. Coronary artery disease: (1) C

ap. Congestive heart failure: (1) C

aq. Elevated uric acid such as gout: (1)

ar. Kidney disease: (1) C

as. Polycystic ovary syndrome: (1)

at. Sleep apnea *(not breathing during sleep):* (1)

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (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. Substance abuse: (1) C

bd. None of the above: (1)

32. Has the patient ever had bariatric surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1) C

b. Jejunoileal *(or other intestinal)* bypass: (1) C

c. Biliopancreatic diversion: (1) C

d. Other GI or bariatric surgery *(specify):* (1)

_____

e. None of the above: (1)

33. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) → Elig No (2)

34. Has the patient received total parenteral nutrition (TPN) in the past 3 years:

Yes (1) → Elig No (2)

35. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) → Elig No (2)

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

Yes (1) No (2)

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. Acetylsalicylic acid (ASA): (1)

b. Aspirin - 325 mg: (1)

c. Demeclocycline (Declomycin): (1)

d. Divalproex (Depakote): (1)

e. Doxycycline (Monodox): (1)

f. Minocycline (Dynacin, Minocin): (1)

g. Oxytetracycline (Terramycin): (1)

h. Tetracycline (Achromycin): (1)

i. Valproate sodium (Depacon): (1)

j. Valproic acid (Depakene): (1)

k. Other known hepatotoxin *(specify):* (1)

_____

l. None of the above: (1)

37. Were any of the items in 36a-k checked:

Yes (*1) → C No (2)

**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): (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)

39. Were any of the items 38a-k checked:

Yes (*1) → C No (2)

**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. Boldenone undecylenate (Equipoise): (1)

b. Fluoxymesterone (Android-F, Halotestin): (1)

c. Methandrostenolone (Dianabol): (1)

d. Methyltestosterone (Android): (1)

e. Nandrolone (Deca-Durabolin, 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)

41. Were any of the items 40a-l checked:

Yes (* 1) → C No (2)

**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:

Yes (1) → EHg No (2)

43. Has the patient used any antidiabetic medications in the past 3 months *(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): (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: (1)

44. Were any of the items 43a-p checked:

Yes (* 1) → C No (2)

**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): (1)

b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)

c. Metformin: (1)

d. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)

e. S-Adenylmethionine (SAM-e): (1)

f. Milk thistle: (1)

g. Probiotics *(any form):* (1)

h. Gemfibrozil (Gen-Fibro, Lopid): (1)

i. Other *(specify):* (1)

_____
specify

j. None of the above: (1)

46. Were any of item 45a-h checked:

Yes (*1) No (2)

C

**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:

Yes (1) No (2)

48. Has the patient taken any vitamin E (either as a supplement or in a multivitamin) in the past 3 months:

Yes (1) No (2)

50.

49. Was/Is the dose of vitamin E greater than 100 IU/day:

Yes (*1) No (2)

C

**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:

Yes (1) No (*2)

Elig

**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:

Yes (1) No (2)

Elig

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): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Other, *(specify):* (1)

_____

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): (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)

j. Simvastatin (Zocor): (1)

k. Other, *(specify):* (1)

_____

l. None of the above: (1)

54. Has the patient taken any antiobesity medications in the past 3 months *(check all that apply):*

a. Dexfenfluramine hydrochloride (Redux): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

c. Methamphetamine hydrochloride (Desoxyn, Gradumet): (1)

d. Orlistat (Xenical): (1)

e. Phendimetrazine tartrate (Adipost, Bontril): (1)

f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): (1)

g. Sibutramine hydrochloride monohydrate (Meridia): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

55. Were any of the items 54a-i checked:

Yes (*1) No (2)

C

**Caution: Use of antiobesity medications in the 3 months prior to randomization is exclusionary.*

L. Use of other medications and supplements

56. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 3 months *(check all that apply):*

a. Acetaminophen (Tylenol): (1)

b. Aspirin - 325 mg: (1)

c. Celecoxib (Celebrex): (1)

d. Ibuprofen (Advil, Motrin): (1)

e. Indomethacin (Indocin): (1)

f. Naproxen (Aleve, Naprosyn): (1)

g. Other, *(specify):* (1)

_____

h. Other, *(specify):* (1)

_____

i. None of the above: (1)

57. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 3 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)

58. Has the patient taken any allergy or asthma medications in the past 3 months that have not already been reported on this form *(check all that apply)*

a. Albuterol: (1)

b. Beclomethasone dipropionate (Beclovent, Vanceril): (1)

c. Budesonide (Pulmicort, Rhinocort): (1)

d. Fluticasone propionate (Flonase, Flovent): (1)

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

g. Triamcinolone acetonide (Azmacort, Nasacort): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None 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 *(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)

l. 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)

60. Has patient taken any of the following medications in the past 3 months *(check all that apply)*

a. Isotretinoin (Accutane): (1)

b. Levonorgestrel (Norplant): (1)

c. Levothyroxine (Levoxyl, Synthroid): (1)

d. Liothyronine (Cytomel): (1)

e. Oral contraceptives: (1)

f. Penicillamine (Cuprimine, Depen): (1)

g. Trientine hydrochloride (Syprine): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. Other, *(specify):* (1)

_____

k. Other, *(specify):* (1)

_____

l. Other, *(specify):* (1)

_____

m. None of the above: (1)

M. Willingness to use effective birth control methods

61. Are you female and of childbearing potential:

Yes (1) No (2)

65.

62. Are you currently pregnant:

Yes (1) No (2)

Elig

63. Are you currently breast feeding:

Yes (* 1) No (2)

C

**Caution: Patient cannot be breastfeeding at time of randomization.*

64. Are you willing to use effective birth control methods during TONIC:

Yes (1) No (2)

Elig

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

TONIC

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.

	Plasma:		Serum:	
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 visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b p 1

7. Study: TONIC 3

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)
23. ___
No, other reason *(specify):* (3)
23. ___

_____
specify other reason

9. Date and time of blood draw

a. Date:

___ ___–___ ___ ___–___ ___
day mon year

b. Time:

___ ___ : ___ ___ (1) (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):*

Yes (1) No (2)
12. ___

11. Attach duplicate CTAD tube label:

TONIC Form. BP, Plas.
Pt: 9999, xyz
Visit vvvv
Date: _____

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):

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. Date and time cryovials frozen in -70°C or -20°C

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Time:
____ ____:____ ____ ($_1$) ($_2$)
hour minute am pm

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 open).
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 form.

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: c g 1

7. Study: TONIC 3

B. Consent for collection, storage, and use of DNA samples for current and future genetic research

8. Does the patient/guardian consent to genetic research on NAFLD that is currently planned by the study investigators:

(Yes 1) (No 2)

9. Does the patient/guardian consent to future genetic research on NAFLD by this study or other study investigators:

(Yes 1) (No 2)

10. Does the patient/guardian consent to future genetic research on liver disease, its complications, and metabolic disorders by this study or other study investigators:

(Yes 1) (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/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 8 through 10; a response of "No" to this question (item 12) means that blood should NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):*

(Yes 1) (No 2)

C. Administrative information

13. Study Physician PIN: ____ ____ ____

14. Study Physician signature:

_____

15. Clinical Coordinator PIN: ____ ____ ____

16. Clinical Coordinator signature:

_____

17. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

TONIC

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. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: f 1 2 0

6. Form & revision: c o 1

7. Study: TONIC_3

B. Database participation

8. Does the patient wish to re-enter or join the NAFLD Database:

Yes (1) No (2)

11.

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: (1)

b. Assent signed by patient (must have guardian sign the consent): (1)

c. Consent signed by guardian: (1)

d. No (*1)

STOP

** Informed consent must be signed*

10. Was the patient previously enrolled in the NAFLD Database:

Yes (*1) No (+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 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

c r 1 6. Form and revision

__ 7. Study: **1**=Database; **2**=PIVENS; **3**=TONIC

__ __ / __ __ __ / __ __ 8. Date of biopsy

B. Slide sequence number

9. 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

16. 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. Microvesicular steatosis, contiguous patches: **0**=Absent; **1**=Present

17. 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

_____ . . . b. Microgranulomas seen: **0**=No; **1**=Yes

_____ . . . c. Large lipogranulomas seen: **0**=No; **1**=Yes

_____ . . . d. Amount of portal, chronic inflammation: **0**=None; **1**=Mild; **2**=More than mild

18. Liver cell injury

_____ . . . a. Ballooning: **0**=None; **1**=Few; **2**=Many

_____ . . . b. Acidophil bodies: **0**=Rare/absent; **1**=Many

_____ . . . c. Pigmented macrophages (*Kupffer cells*): **0**=Rare/absent; **1**=Many

_____ . . . d. Megamitochondria: **0**=Rare/absent; **1**=Many

_____ 19. Mallory's hyaline: **0**=Rare/absent; **1**=Many

_____ 20. Glycogen nuclei: **0**=Rare/absent; **1**=Many

Masson's trichrome stain

_____ 21. Fibrosis stage: **0**=None; **1a**=Mild, zone 3 perisinusoidal (*requires trichrome*);
1b=Moderate, zone 3, perisinusoidal (*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 grade: **0**=Absent or barely discernible, 40x ➜ **GOTO item 22c**;
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 23**; **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

_____ 23. Is this steatohepatitis? **0**=No; **1a**=Suspicious/borderline/indeterminate: Zone 3 pattern;
1b=Suspicious/borderline/indeterminate: Zone 1, periportal pattern; **2**=Yes, definite

_____ 24. Is cirrhosis present? **0**=No ➜ **GOTO item 27**; **1**=Yes

_____ 25. Is this cryptogenic cirrhosis: **0**=No ➜ **GOTO item 27**; **1**=Yes

26. Features suggestive of steatohepatitis etiology for cryptogenic cirrhosis:

_____ . . . a. Mallory's hyaline (*rule out cholate stasis*): **0**=Absent; **1**=Present

_____ . . . b. Perisinusoidal fibrosis away from septa: **0**=Absent; **1**=Present

_____ . . . c. Hepatocyte ballooning: **0**=Absent; **1**=Present

_____ . . . d. Megamitochondria: **0**=Absent; **1**=Present

_____ . . . e. Other notable findings: **0**=Absent; **1**=Present; Specify: _____

27. Other comments: _____

TONIC

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: d r 1

7. Study: TONIC_3

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Health care provider or NASH CRN staff: (1)
d. Newspaper: (1)
e. Funeral parlor/home: (1)
f. Medical record: (1)
g. Medical examiner: (1)
h. Coroner: (1)
i. Other *(specify):* (1)

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

11. Cause of death
(Study Physician: use whatever knowledge you have and your best medical judgment to best characterize the cause of death; check only one):

Heart disease (1)
Stroke (2)
Liver disease (3)
Malignancy (4)
Other *(specify):* (5)

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

TONIC

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: d x 1

7. Study: TONIC 3

B. DEXA scan information

8. Did the patient have a whole body dual energy x-ray absorptiometry (DEXA) scan:

(Yes 1) (No 2)

10. ____

9. Specify why DEXA scan was not performed

a. Patient is too heavy: (1)
b. Scanner is broken: (1)
c. Other *(specify):* (1)

_____
specify

14. ____

10. DEXA scanner used:

Hologic QDR 4500A (1)
Hologic QDR 4500W (2)
Hologic New Discovery Series 12.3 (3)
Hologic Delphi QDR Series (4)
Hologic Delphi W (5)
Lunar Prodigy (6)
Other *(specify)* (7)

_____
specify make & model

C. DEXA results summary

11. Date of DEXA scan:

____ ____–____ ____ ____–____ ____
day mon year

12. Trunk % fat *(if your scanner reports both tissue % fat and region % fat, record region % fat on this report):*

____ ____ • ____ ____
%

13. Total % fat *(if your scanner reports both tissue % fat and region % fat, record region % fat on this report):*

____ ____ • ____ ____
%

C. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

TONIC

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 Elig 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: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: r z ____ ____

6. Form & revision: e c 1

7. Study: TONIC 3

B. Alcohol use exclusion

8. Does the patient have a history of significant alcohol intake:

( ) Yes 1 — Elig
( ) No 2

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:

( ) Yes 1
( ) No 2 — Elig

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:

( ) Yes 1
( ) No 2 — Elig

C. Cirrhosis exclusion

11. Clinical cirrhosis evaluation

a. Does the patient have varices or ascites and does the Study Physician judge that the patient has cirrhosis:

Yes (1) No (2) Elig

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):*

Yes (1) No (2) Elig

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:

Yes (1) No (2) Elig

b. In the Study Physician's judgment, does the patient have a history of autoimmune hepatitis:

Yes (1) No (2) Elig

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:

Yes (1) No (2) Elig

14. Does the patient have alpha-1 antitrypsin (A1AT) deficiency confirmed by A1AT level less than normal *(physician judgment):*

Yes (1) No (2) Elig

15. Does the patient have an iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:

Yes (1) No (2) Elig

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:

Yes (1) No (2) Elig

b. Known bile duct obstruction:

Yes (1) No (2) Elig

c. Any other type of liver disease other than NAFLD that warrants exclusion from the trial:

Yes (1) No (2) Elig

E. Other medical exclusions

17. History of metabolic acidosis:

Yes (1) No (2) Elig

18. History of renal dysfunction:

Yes (1) No (2) Elig

19. History of coagulopathy:

Yes (1) No (2) Elig

20. History of diabetes mellitus:

Yes (1) No (2) Elig

21. History of bariatric surgery *(jejunoileal bypass or gastric weight loss surgery):*

Yes (1) No (2) Elig

22. History of hepato-biliary surgery:

( ) Yes (1) → Elig ( ) No (2)

23. Inability to safely undergo liver biopsy:

( ) Yes (1) → Elig ( ) No (2)

24. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the 2 years prior to screening:

( ) Yes (1) → Elig ( ) No (2)

25. Use of antidiabetic drugs in the 3 months prior to randomization:

( ) Yes (1) → Elig ( ) No (2)

26. Use of antiNAFLD drugs in the 3 months prior to randomization:

( ) Yes (1) → Elig ( ) No (2)

27. Use of antiobesity drugs in the 3 months prior to randomization:

( ) Yes (1) → Elig ( ) No (2)

28. Use of Vitamin E at a dose greater than 100 IU/day in the 3 months prior to randomization:

( ) Yes (1) → Elig ( ) No (2)

29. Known active, serious medical disease with a likely life-expectancy less than 5 years:

( ) Yes (1) → Elig ( ) No (2)

30. Known active substance abuse, such as alcohol or inhaled or injection drugs in the year prior to screening:

( ) Yes (1) → Elig ( ) No (2)

31. Other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study:

( ) Yes (1) → Elig ( ) No (2)

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 ( ) (2) → Elig

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):*

( ) Yes (1) ( ) No (2) → Elig

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 on the day of randomization.)

34. Was an ineligibility condition checked or an eligibility not ascertained in items 8-33:

( ) Yes (1) ( ) No (*2)

43. ____

**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) → **43.**

No (2)

Task not run because patient is known to be ineligible (3) → **43.**

36. Does the patient feel well today:

Yes (1) → STOP

No (*2)

**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:

Yes (1) → **41.**

No (2)

38. Is the patient of childbearing potential:

Yes (*1) → **40.**

No (2)

**Administer pregnancy test.*

39. Is the patient pregnant *(positive pregnancy test on the day of randomization):*

Yes (*1) → Elig

No (2)

**Go to item 43.*

40. Is the patient currently breast feeding:

Yes (*1) → Elig

No (2)

**Go to item 43.*

41. Per the Study Physician's judgment, is there any reason to exclude the patient from randomization:

Yes (*1) → Elig

No (2)

**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):*

Yes (*1) → **44.**

No (†2) → Elig

**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.

I. Reasons for ineligibility for ineligible patients

Note: Complete this section for ineligible patients only.

43. Reason for ineligibility *(check all that apply)*

a. Reason covered in items 8-42: (1)

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 steatosis: (1)

e. Creatinine ≥ 1.5 mg/dL for males or creatinine ≥ 1.4 mg/dL for females: (1)

f. Positive for hepatitis B: (1)

g. Positive for hepatitis C: (1)

h. ALT< 60 U/L: (1)

i. ALT > 400 U/L: (1)

j. Fasting serum glucose ≥ 126 mg/dL or 2 hour serum glucose ≥ 200 mg/dL: (1)

k. Known intolerance to metformin: (1)

l. Known intolerance to vitamin E: (1)

m. Liver transplant: (1)

n. Currently being evaluated for bariatric surgery: (1)

o. TPN in the past 3 years prior to screening: (1)

p. Inability to swallow study medication: (1)

q. Tests are outside time window and clinic chose not to repeat tests: (1)

r. Other reason not covered on this form *(specify):* (1)

_____
specify

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.)

TONIC

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: f i 1

7. Study: TONIC 3

B. Study identifiers of sibling(s) of the index patient recorded in section A

8. How many siblings of the index patient identified in item 2 are enrolled in TONIC, PIVENS, or NAFLD Database *(if no siblings, code "0" and skip to item 14; call the DCC if more than 5 siblings are enrolled in TONIC, PIVENS, or NAFLD Database):*

____
0-5

If zero (0), then skip to item 14.

9. First sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 14 if there are no more siblings enrolled in TONIC, PIVENS, or NAFLD Database.

10. Second sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 14 if there are no more siblings enrolled in TONIC, PIVENS, or NAFLD Database.

11. Third sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 14 if there are no more siblings enrolled in TONIC, PIVENS, or NAFLD Database.

12. Fourth sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Skip to item 14 if there are no more siblings enrolled in TONIC, PIVENS, or NAFLD Database.

13. Fifth sibling

a. Patient ID: ____ ____ ____ ____

b. Patient code: ____ ____ ____

c. Biological relationship to index patient *(select one):*

Full (1)
Half (2)
Not biological (3)

Call the DCC for instructions if there are more siblings enrolled in TONIC, PIVENS, or NAFLD Database.

C. Study identifiers of the parents of the index patient recorded in section A *(call the DCC if more than 1 mother and/or 1 father are enrolled in PIVENS or NAFLD Database)*

14. Mother of index patient

a. Is the mother of the index patient enrolled in PIVENS or NAFLD Database:

Yes (1) No (2)

15.

b. Patient ID: ____ ____ ____ ____

c. Patient code: ____ ____ ____

d. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

15. Father of index patient

a. Is the father of the index patient enrolled in PIVENS or NAFLD Database:

Yes (1) No (2)

16.

b. Patient ID: ____ ____ ____ ____

c. Patient code: ____ ____ ____

d. Biological relationship to index patient *(select one):*

Full (1)
Not biological (2)

D. Administrative information

16. Clinical coordinator PIN: ____ ____ ____

17. Clinical coordinator signature:

_____

18. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

TONIC

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: h i 1

7. Study: TONIC 3

B. Interval identification

8. Date of last Followup Medical History form *(if this is visit f004 then date of s1):*

____ ____–____ ____ ____–____ ____
day mon year

9. Visit code of last Followup Medical History form *(if this is visit f004 then s1):*

____ ____ ____ ____

C. NAFLD evaluation

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

(* Yes 1) (No 2)

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

D. Alcohol consumption (AUDIT-C) since the last visit *(interview with patient)*

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

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

14. ____

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

13. 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. Tobacco cigarette smoking *(interview with patient)*

14. Since the last visit, have you smoked tobacco cigarettes regularly *("No" means less than 1 day per week on average):*

(Yes 1) (No 2)

17.

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)*

a. Diabetes type 1: (1)

b. Diabetes type 2: (1)

c. Gestational diabetes *(diabetes of pregnancy):* (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. Hemochromatosis or iron overload: (1)

k. Drug induced liver disease: (1)

l. 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. Metabolic acidosis: (1)

r. Ascites: (1)

s. Edema: (1)

t. Hepatic encephalopathy: (1)

u. Portal hypertension: (1)

v. Hepatorenal syndrome: (1)

w. Hepatopulmonary syndrome: (1)

x. Short bowel syndrome: (1)

y. Hemophilia *(bleeding disorder):* (1)

z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

aa. Endocrine disease *(hormonal abnormality):* (1)

ab. Hepatocellular carcinoma: (1)

ac. Other malignancy *(cancer):* (1)

ad. Human immunodeficiency virus (HIV): (1)

ae. Peripheral neuropathy: (1)

af. Seizure disorder or epilepsy: (1)

ag. Drug allergies: (1)

ah. Hypothyroidism: (1)

ai. Hypertension: (1)

aj. Cerebrovascular disease: (1)

ak. Dysbetalipoproteinemia: (1)

al. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

am. Pancreatitis: (1)

an. Cholelithiasis: (1)

ao. Coronary artery disease: (1)

ap. Congestive heart failure: (1)

aq. Elevated uric acid such as gout: (1)

ar. Kidney disease: (1)

as. Polycystic ovary syndrome: (1)

at. Sleep apnea *(not breathing during sleep):* (1)

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (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. Substance abuse: (1)

bd. None of the above: (1)

18. Since the last visit, has the patient had bariatric surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1)

b. Jejunoileal *(or other intestinal)* bypass: (1)

c. Biliopancreatic diversion: (1)

d. Other GI or bariatric surgery, *(specify):* (1)

_____

e. None of the above: (1)

19. Since the last visit, has the patient received an organ, limb, or bone marrow transplant:

(Yes 1) (No 2)

20. Since the last visit, has the patient received total parenteral nutrition (TPN):

(Yes 1) (No 2)

21. Since the last visit, has the patient been hospitalized:

(Yes 1) (No 2)

22. ____

If Yes, specify reason:

_____
specify

22. Since the last visit, has the patient had any serious health problem not already reported:

(Yes 1) (No 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): (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: (1)

24. Since the last visit, has the patient taken any lipid lowering medications *(check all that apply):*

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

_____

m. None of the above: (1)

25. Since the last visit, has the patient taken any antiobesity medications *(check all that apply):*

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

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

26. Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications *(check all that apply):*

a. Acetaminophen (Tylenol): (1)
b. Aspirin - 325 mg: (1)
c. Celecoxib (Celebrex): (1)
d. Ibuprofen (Advil, Motrin): (1)
e. Indomethacin (Indocin): (1)
f. Naproxen (Aleve, Naprosyn): (1)
g. Valdecoxib (Bextra): (1)
h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

27. Since the last visit, has the patient taken any histamine H2 receptor antagonists or 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): (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)

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): (1)
e. Loratadine (Claritin): (1)
f. Mometasone furoate (Nasonex): (1)
g. Triamcinolone acetonide (Azmacort, Nasacort): (1)
h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. None of the above: (1)

31. Since the last visit, has the patient taken a multivitamin regularly:

Yes (1) No (2)

32. Since the last visit, has the patient taken vitamins other than multivitamins *(do not include TONIC study medication):*

Yes (1) No (2)

35. ____

33. Which vitamins has the patient taken *(check all that apply):*

a. Vitamin B (any type): (1)
b. Vitamin C: (1)
c. Vitamin D: (1)
d. Vitamin E (alpha-tocopherol): (1)
e. Other, *(specify):* (1)

_____

34. Is the patient currently taking vitamin E at a dose greater than 100 IU/day *(do not include TONIC study medication):*

Yes (*1) No (2)

**Remind patient not to take vitamin E supplements at doses greater than 100 IU/day during TONIC.*

35. Since the last visit, has the patient taken any supplements *(check all that apply):*

a. Alpha-lipoic acid: (1)
b. Beta-carotene: (1)
c. Betaine (Cystadane): (1)
d. Calcium (any form): (1)
e. Carnitine (any form): (1)
f. Chondroitin (any form): (1)
g. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
h. Cod liver oil: (1)
i. Coenzyme Q: (1)
j. Dichloroacetate: (1)
k. Echinacea: (1)
l. Fish oil (any form): (1)
m. Flax seed oil: (1)
n. Garlic: (1)
o. Ginkgo biloba: (1)
p. Glucosamine (any form): (1)
q. Lecithin: (1)
r. Magnesium: (1)
s. Milk thistle: (1)
t. N-acetyl-cysteine: (1)
u. Potassium (any form): (1)
v. Probiotics (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)

_____

ad. Other, *(specify):* (1)

_____

ae. None of the above: (1)

36. 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. Acetylsalicylic acid (ASA): (1)
b. Aspirin - 325 mg: (1)
c. Demeclocycline (Declomycin): (1)
d. Divalproex (Depakote): (1)
e. Doxycycline (Monodox): (1)
f. Isotretinoin (Accutane): (1)
g. Levonorgestrel (Norplant): (1)
h. Levothyroxine (Levoxyl, Synthroid): (1)
i. Liothyronine (Cytomel): (1)
j. Minocycline (Dynacin, Minocin): (1)
k. Oral contraceptives: (1)
l. Oxytetracycline (Terramycin): (1)
m. Penicillamine (Cuprimine, Depen): (1)
n. Tetracycline (Achromycin): (1)
o. Trientine hydrochloride (Syprine): (1)
p. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)
q. Valproate sodium (Depacon): (1)
r. Valproic acid (Depakene): (1)
s. Other, *(specify):* (1)

_____

t. Other, *(specify):* (1)

_____

u. Other, *(specify):* (1)

_____

v. Other, *(specify):* (1)

_____

w. Other, *(specify):* (1)

_____

x. None of the above: (1)

H. Administrative information

37. Study Physician PIN: ____ ____ ____

38. Study Physician signature:

_____

39. Clinical Coordinator PIN: ____ ____ ____

40. Clinical Coordinator signature:

_____

41. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

TONIC

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: i e 1

7. Study: TONIC 3

B. Visit interval identification

8. Most recently completed visit (screening or followup)

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____ ____

C. Patient information

9. Date randomized in TONIC *(enter n if patient is not yet randomized):*

____ ____–____ ____ ____–____ ____
day mon year

10. Gender:

Male (1)
Female (2)

11. Age at time of event: ____ ____
years

12. Is the patient currently receiving the metformin-series study drug:

Yes (1) No (2)

13. Is the patient currently receiving the vitamin E-series study drug:

Yes (1) No (2)

14. Summarize the patient's history of treatment with TONIC study drugs *(eg, how long has patient been on study drugs, have there been any treatment interruptions):*

_____

_____

_____

_____

_____

_____

D. Event description

15. Is the event associated with TONIC study drugs:

Yes (1) No (2)

18.

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)*

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.*

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)

_____

_____

22. Severity grade *(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 Serious Adverse Event Report (AN) to report serious and unexpected adverse events or call the DCC if unsure what to do):*

Not applicable	(0)
Grade 1 - Mild	(1)
Grade 2 - Moderate	(2)
Grade 3 - Severe	(3)
Grade 4 - Life threatening or disabling	(4)
Grade 5 - Death	(*5)

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

23. Date event resolved *(enter n if event is not yet resolved):*

____ ____–____ ____ ____–____ ____
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:

____ ____–____ ____ ____–____ ____
day mon year

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.

TONIC

LP – Symptoms of Liver Disease (Children)

Purpose: To obtain the patient's view of his/her liver disease symptoms.
When: Visits s2, f048, f096, and f120.
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 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.

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: **1 p 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient/parent (1)
→ **10.**
Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that 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

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
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 affects you *(choose only one)*:

Circle one

I feel normal and am not tired **(If this is how you feel, please circle "1" and go 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 2
At least part of several days a week 3
At least part of one day a week 4
Not as much as above 5

15. Are you tired *(choose only one)*:

When you wake up in the morning 1
Or does it come on with the day 2
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
No 2

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.

TONIC

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 (FAIL) 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: l r 1

7. Study: TONIC 3

B. Initial screening ALT

8. Is this visit s1:

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

11.

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):

____ ____–____ ____ ____–____ ____
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):*

____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

b. Lower limit of normal: ____ ____ ____
U/L

C. Hematology

Required at visits s1, f024, f048, f072, f096, and f120.

11. Is hematology testing required at this visit:

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

17.

12. Date of blood draw for hematology:

____ ____–____ ____ ____–____ ____
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).

13. Hemoglobin: ____ ____ • ____
g/dL

14. Hematocrit: ____ ____ • ____
%

15. White blood cell count (WBC):

____ ____ • ____
10^3 cells/ µL or 10^9 cells/L

16. Platelet count:

____ ____ ____,____ ____ ____
cells/ µL

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:

____ ____–____ ____ ____–____ ____
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).

18. Sodium: ____ ____ ____ mEq/L

19. Potassium: ____ ____ • ____ mEq/L

20. Chloride: ____ ____ ____ mEq/L

21. Bicarbonate: ____ ____ • ____ mEq/L

22. Calcium: ____ ____ • ____ mg/dL

23. Phosphate: ____ ____ • ____ mg/dL

24. Blood urea nitrogen (BUN): ____ ____ 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: ____ ____ • ____ mg/dL

27. Albumin: ____ • ____ g/dL

28. Total protein: ____ ____ • ____ g/dL

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:

Yes (1) No (2)

31.

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

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:

Yes (1) No (2)

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 1) (No 2)

41.

35. Date of blood draw for hepatic panel:

____ ____–____ ____ ____–____ ____
day mon year

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

36. Bilirubin (total): ____ ____ • ____
mg/dL

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 B_{12}

Required at visits f024, f048, f072, f096, and f120.

41. Is vitamin B_{12} required at this visit:

(Yes 1) (No 2)

44.

42. Date of blood draw for vitamin B_{12}:

____ ____–____ ____ ____–____ ____
day mon year

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

43. Vitamin B_{12} (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:

(Yes 1) (No 2)

50.

45. Date of blood draw for prothrombin time, GGT, and HbA1c:

____ ____–____ ____ ____–____ ____
day mon year

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

46. Prothrombin time (PT): ____ ____ • ____
sec

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 (1)
No (2)
54.
No, patient is diabetic (3)
54.

51. Date of blood draw for OGTT:

____ ____–____ ____ ____–____ ____
day mon year

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: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ µU/mL

c. Serum C peptide: ____ ____ • ____ ng/mL

53. OGTT results at 2 hours

a. Serum glucose: ____ ____ ____ mg/dL

b. Serum insulin: ____ ____ ____ • ____ µU/mL

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:

Yes (1) No (2)
59.

55. Date of blood draw for free fatty acid, leptin and C-reactive protein (all serum):

____ ____–____ ____ ____–____ ____
day mon year

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

57. Leptin: ____ ____ • ____ ng/mL

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:

Yes (1) No (2)
62.

60. Date of urine collection (or blood draw):

____ ____–____ ____ ____–____ ____
day mon year

Date must be the same day as date of visit.

61. Pregnancy test results *(if pregnancy test is positive at s1, patient is ineligible):*

Positive (1)
Negative (2)

M. Eligibility check

62. Is this the s1 visit:

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

64.

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):

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

Elig

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

TONIC

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 Elig is checked for any item the patient is not eligible for the TONIC trial. If C 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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:
____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: 1 s 1

7. Study: TONIC 3

B. Screening etiologic tests

8. Date of blood draw for serological assays to exclude viral causes of chronic liver disease:
____ ____–____ ____ ____–____ ____
day mon year
Repeat if date is greater than 1 year prior to screening.

a. Hepatitis B surface antigen (HBsAg):
Positive (1) Elig
Negative (2)

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 (1)
Negative (2)
Not available (3)

d. Hepatitis C antibody (anti-HCV) *(indicate result as negative if EIA is positive but RIBA is negative):*
Positive (1) Elig
Negative (2)

e. Hepatitis C virus RNA (HCV RNA):
Positive (1) Elig
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 (* 1)
Negative (2)

12.

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

Yes (* 1) No (2)

C

** Check Liver Biopsy Histology Findings Form for autoimmune liver disease.*

12. Antismooth muscle antibody (ASMA):

Positive (* 1)
Negative (2)

13.

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 (* 1)
Negative (2)

15.

Not available (3)

15.

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

Yes (* 1) No (2)

C

** Check Liver Biopsy Histology Findings Form for primary biliary cirrhosis.*

D. Ceruloplasmin

15. Date of blood draw for ceruloplasmin:

____ ____–____ ____ ____–____ ____
day 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:

Yes (* 1) No (2)

C

** 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):

Yes (1) No (2)

Elig

F. Iron

19. Date of blood draw for hemochromatosis screening:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 5 years prior to screening.

a. Iron: ____ ____ ____ µg/dL

b. Total Iron Binding Capacity: ____ ____ ____ µg/dL

c. Ferritin: ____ ____ ____ ____ ng/mL

20. Is hepatic iron index available:

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

22.

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 year

TONIC

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 ⊘ 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: 1 u 1

7. Study: TONIC 3

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 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.

8. Date of blood draw for hepatic panel:

____ ____–____ ____ ____–____ ____
day mon year

9. Bilirubin (total): ____ ____ • ____
mg/dL

10. Bilirubin (conjugated or direct):

____ • ____
mg/dL

11. Aspartate aminotransferase (AST)

____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

b. Lower limit of normal: ____ ____ ____
U/L

12. Alanine aminotransferase (ALT) *(if ALT ≤ 60 U/L, patient is ineligible; patient is also ineligible if the ALT done closest in time to randomization is > 400 U/L)*

____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

b. Lower limit of normal: ____ ____ ____
U/L

13. Alkaline phosphatase ____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

b. Lower limit of normal: ____ ____ ____
U/L

C. Vitamin B_{12}, free fatty acid, leptin, and C-reactive protein

14. Date of blood draw for vitamin B_{12}, free fatty acid, leptin, and C-reactive protein (all on serum):

____ ____–____ ____ ____–____ ____
day mon year

Date must be within 3 months of screening.

15. Vitamin B_{12} *(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):*

____ ____ ____ • ____
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 screening.

20. Prothrombin time (PT): ____ ____ • ____
sec

21. International normalized ratio (INR):

____ • ____

22. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

23. HbA1c: ____ ____ • ____
%

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

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: ____ ____ ____ • ____
µU/mL

c. Serum C peptide: ____ ____ • ____
ng/mL

26. OGTT results at 2 hours *(if 2-hour glucose ≥ 200 mg/dL, patient is ineligible)*

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____
µU/mL

F. Pregnancy test

27. Is pregnancy test applicable:

Yes (1) No (2)

30.

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 at s1 or s2, patient is ineligible):*

Positive (1)
Negative (2)

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):

( ) Yes 1 → Elig

( ) No 2

H. 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

TONIC

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.

A. Center, patient, and visit identification

1. Center ID: ___ ___ ___ ___

2. Patient ID: ___ ___ ___ ___

3. Patient code: ___ ___ ___

4. Date of visit (date patient completed the form):

___ ___ - ___ ___ ___ - ___ ___
day month year

5. Visit code: ___ ___ ___ ___

6. Form & revision: **m a 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by the Clinical Coordinator after survey is completed).

8. How was the questionnaire completed:
Self-administered by patient/parent (1)
10.
Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that apply)*
a. Patient: (1)
b. Patient's mother or female guardian: (1)
c. Patient's father or male guardian: (1)
d. Other, *specify*: (1)
_____

10. Clinical Coordinator
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 3
6 to 8 days 4
9 or more days 5

13. How many times in the past 14 days have you done at least 20 minutes of light exercise that was not 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 3
6 to 8 days 4
9 or more days 5

14. During a normal week how many hours a day 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 sports or activities did you participate in on a competitive 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 5

What activities did you compete in?

_____

_____

_____

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

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

16. Check all activities that you did at least 10 times in the **PAST YEAR**. Do not include time spent in school physical education classes. Include all sport teams that you participated in during the last year.

( ) 01. Aerobics	( ) 02. Band/Drill Team	( ) 03. Baseball
( ) 04. Basketball	( ) 05. Bicycling	( ) 06. Bowling
( ) 07. Cheerleading	( ) 08. Dance Class	( ) 09. Football
( ) 10. Garden/Yard Work	( ) 11. Gymnastics	( ) 12. Hiking
( ) 13. Ice Skating	( ) 14. Roller Skating	( ) 15. Running and Exercise
( ) 16. Skateboarding	( ) 17. Snow Skiing	( ) 18. Soccer
( ) 19. Softball	( ) 20. Street Hockey	( ) 21. Swimming
( ) 22. Tennis	( ) 23. Volleyball	( ) 24. Water Skiing
( ) 25. Weight Training (Competitive)	( ) 26. Wrestling	( ) 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.

Activity Code #	Activity	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Months per Year	Days per Week	Minutes per Day
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __
__ __														__ __	__	__ __ __

17. Today's date: ________________________________

TONIC

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: m r 1

7. Study: TONIC 3

B. Upper abdominal MRI

8. Date of upper abdominal MRI:

____ ____ – ____ ____ ____ – ____ ____
day mon year

9. Findings suggestive of NAFLD, cryptogenic 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. Splenomegaly: (1)
j. Ascites: (1)
k. Other features of portal hypertension *(specify):* (1)

_____

_____

l. Other abnormality *(specify):* (1)

_____

_____

m. None of the above: (1)

C. Administrative information

10. Study Physician PIN: ____ ____ ____

11. Study Physician signature:

_____

12. Clinical Coordinator PIN: ____ ____ ____

13. Clinical Coordinator signature:

_____

14. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

TONIC

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.

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: f ____ ____ ____

6. Form & revision: m v 1

7. Study: TONIC 3

B. Reason for completion of this form

8. Was the entire visit missed:
(Yes 1) (No 2)
11. ____

C. Missed visit information

9. Reason for missed visit *(check all that apply)*

a. Patient was ill: (1)

b. Patient was temporarily away from area: (1)

c. Patient refused to return: (1)

d. Patient has permanently moved from the area: (1)

e. Unable to contact patient: (1)

f. Other *(specify):* (1)

_____
specify

10. Steps taken to avoid missing the visit *(check all that apply)*

a. Telephoned patient: (1)

b. Mailed reminder card: (1)

c. Other *(specify):* (1)

_____
specify

14. ____

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)

l. 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. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

TONIC

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: p e 1

7. Study: TONIC_3

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement:

____ ____ ____ • ____

b. Weight, 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
waist circumference

c. Units:

Inches (1)
Centimeters (2)

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)*

a. Circumference, 1st measurement:

___ ___ ___ • ___
hip circumference

b. Circumference, 2nd measurement:

___ ___ ___ • ___
hip circumference

c. Units:

Inches (1)
Centimeters (2)

12. Triceps *(right arm, with elbow extended and arm relaxed; repeat skin fold measurements until you have two within 10 mm of each other; repeat mid-upper arm circumference until you have two within 1.5 in (3.8 cm) of each other)*

a. Skin fold, 1st measurement:

___ ___ ___ • ___
mm

b. Skin fold, 2nd measurement:

___ ___ ___ • ___
mm

c. Mid-upper arm circumference, 1st measurement:

___ ___ • ___
arm circumference

d. Mid-upper arm circumference, 2nd measurement:

___ ___ • ___
arm circumference

e. Units for arm circumference:

Inches (1)
Centimeters (2)

13. Temperature *(Oral)*

a. Degrees: ___ ___ ___ • ___

b. Scale:

Fahrenheit (1)
Centigrade (2)

14. Blood pressure

a. Systolic: ___ ___ ___
mmHg

b. Diastolic: ___ ___ ___
mmHg

15. Resting radial pulse: ___ ___ ___
beats/minute

16. Respiratory rate: ___ ___
breaths/minute

C. Examination findings

17. Skin:

Normal (1)
20.
Abnormal (2)

18. Acanthosis nigricans *(check only one):*

Absent *(not detectable on close inspection)* (0)

Present *(clearly present on close inspection, not visible to casual observer, extent not measurable)* (1)

Mild *(limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth)* (2)

Moderate *(extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front)* (3)

Severe *(extending anteriorly, > 6 inches in breadth, visible from front)* (4)

19. Other skin abnormality *(check all that apply)*

a. Jaundice: (1)
b. Palmar erythema: (1)
c. Spider angiomata: (1)
d. Other *(specify):* (1)

_____

e. None of the above: (1)

20. Head, eyes, ears, nose, throat:

Normal (1)
22.
Abnormal (2)

21. Abnormality of the head, eyes, nose, throat
(check all that apply)

a. Jaundice: (1)
b. Other *(specify):* (1)

_____
specify

22. Neck:

Normal (1)
23.
Abnormal (2)

specify abnormality

23. Lymphatic:

Normal (1)
24.
Abnormal (2)

specify abnormality

24. Chest and lungs:

Normal (1)
25.
Abnormal (2)

specify

25. Heart:

Normal (1)
26.
Abnormal (2)

specify abnormality

26. Abdomen:

Normal (1)
28.
Abnormal (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)
30.
Abnormal (2)

29. Abnormality of liver or spleen *(check all that apply)*

a. Hepatomegaly: (1)
(if checked, span from right midclavicular line):
___ ___ • ___
cm

b. Splenomegaly: (1)

c. Other *(specify):* (1)

specify

30. Extremities:

Not performed (0)
32.
Normal (1)
32.
Abnormal (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)

e. Other *(specify):* (1)

specify

32. Genitourinary/pelvis:

Not performed (0)
33.
Normal (1)
33.
Abnormal (2)

specify

33. Nervous system:

Not performed (0)
35.
Normal (1)
35.
Abnormal (2)

34. Abnormality of the nervous system *(check all that apply):*

a. Mental status abnormal: (1)

b. Asterixis: (1)

c. Other *(specify):* (1)

_____
specify

D. Tanner Staging

35. Is Tanner staging required for this participant *(Note: Required at screening visit.) (check only one):*

Yes, participant has not reached full sexual maturity or is 17 years old or younger: (1)

No, participant is over 17 years old or had reached full sexual maturity *(Tanner stage 5 on all parameters at screening or for 2 consecutive visits)* (2)

44.

36. Is the patient female: Yes (1) No (2)

40.

Male Tanner Staging

37. Genital stage: ____ 1-5

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

39. Pubic hair stage: ____ 1-5

44.

Female Tanner Staging

40. Breast stage: ____ 1-5

41. Pubic hair stage: ____ 1-5

42. Has menarche occurred: Yes (1) No (2)

44.

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

____ ____
age in years

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 placebo 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 (1)

No, patient was unable to swallow the capsule (2)

Elig

Did not ask for a demonstration at this time (3)

F. Administrative information

45. Study Physician PIN: ___ ___ ___

46. Study Physician signature:

_____

47. Clinical Coordinator PIN: ___ ___ ___

48. Clinical Coordinator signature:

_____

49. Date form reviewed:

___ ___ – ___ ___ ___ – ___ ___
day mon year

TONIC

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: p f 1

7. Study: TONIC 3

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

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)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:

Fahrenheit: (1)
Centigrade: (2)

13. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

14. Resting radial pulse: ___ ___ ___ beats/minute

15. Respiratory rate: ___ ___ breaths/minute

C. Liver signs

16. Liver and spleen:

Normal (1)

18. ___

Abnormal (2)

17. Abnormality *(check all that apply)*

a. Ascites: (1)

b. Asterixis: (1)

c. Contractures: (1)

d. Hepatomegaly: (1)

If Yes, span from right midclavicular line:

___ ___ • ___ cm

e. Jaundice: (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

D. Administrative information

18. Study Physician ID: ___ ___ ___

19. Study Physician signature:

_____

20. Clinical Coordinator ID: ___ ___ ___

21. Clinical Coordinator signature:

_____

22. Date form reviewed:

___ ___–___ ___ ___–___ ___
day mon year

TONIC

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p q 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

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

SOCIAL 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

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. 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.

TONIC

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 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p r 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

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

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

SOCIAL 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

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. 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.

TONIC

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p w 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day 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...)*	**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

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.

Keyed: ( )

TONIC

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **p y 1**

7. Study: TONIC 3

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

Affix label here

Patient ID: __ __ __ __

Patient code: __ __ __

Visit code: __ __ __ __

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

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 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

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.

TONIC

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, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: r c 1

7. Study: TONIC_3

B. TONIC participation

8. Date in item 4 of original TONIC RG form:

____ ____ – ____ ____ ____ – ____ ____
day mon year

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature:

_____

11. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

TONIC

RD – Study Drug Dispensing and Return

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: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____-____ ____ ____-____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: **r d 1**

7. Study: TONIC 3

B. Study drug dispensing

8. Is this a second form for returning additional drug bottles at this visit: Yes (1) No (2)

→ **16.**

9. Will study drug be dispensed today: Yes (1) No (2)

→ **11.**

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: (1)
- **d.** Other *(specify)*: (1)

_____
specify

→ **16.**

TM series

Bottle tear-off label

11.

Affix label here

12.

Affix label here

TE series

13.

Affix label here

14.

Affix label here

15. How were the study drugs dispensed to the patient *(check only one)* :

In person	(1)
Mail	(2)
Other *(specify)*	(3)

_____
specify

C. Study drug return

16. Were any TM series bottles returned at this visit:

Yes (1) No (2)

→ **22.**

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 ___ ___ ___ ___	___ ___ ___ (00-100)
21.	TM ___ ___ ___ ___	___ ___ ___ (00-100)

22. Were any TE series bottles returned at this visit:

Yes (1) No (2)

28. ◄

23. Number of TE series bottles returned *(if more than 4 bottles returned, complete a second RD form)*:

(1-4)

	a. Bottle No.	**b. Number of softgels returned**
24.	TE ___ ___ ___ ___	___ ___ ___ (00-100)
25.	TE ___ ___ ___ ___	___ ___ ___ (00-100)
26.	TE ___ ___ ___ ___	___ ___ ___ (00-100)
27.	TE ___ ___ ___ ___	___ ___ ___ (00-100)

D. Remaining bottles

28. Are any additional bottles being returned:

Yes (* 1) No (2)

**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 year

TONIC

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 Elig is checked for any item, the patient is not eligible for TONIC and the form should not be keyed.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s 1 ____ ____

6. Form & revision: r g 1

7. Study: TONIC 3

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:

Yes (1) No (2) STOP

9. Has the patient's guardian signed the TONIC informed consent statement:

Yes (1) No (2) STOP

10. Has the patient signed the TONIC informed assent statement:

Yes (1)
No (2) STOP
Not using assent (3)
Not using assent for this age child (4)

C. Information about patient

11. Date of birth:

____ ____–____ ____ ____–____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

12. Age at last birthday: ____ ____
years

13. Is the patient's age at least 8 years old and less than 18 years:

Yes (1) No (2) Elig

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 Hispanic, Latino, or Latina origin best *(show the patient/guardian Flash Card #1 and ask the respondent to pick the subcategory that best describes the patient's 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

17. Racial category *(show the patient/guardian Flash Card #2 and ask the respondent to pick the category or categories that describe the patient best; check all that apply)*

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)

18. In what country was the patient born *(check only one):*

Continental US (includes Alaska) or Hawaii	(1)
Other, *(specify):*	(2)

_____
specify

19. Patient's current grade level in school (or home school) *(show the patient/guardian Flash Card #3 and ask the respondent to pick the category that describes the patient best; if summer time, report grade entering in the fall; check only one):*

Grades 1 to 5	(1)
Grades 6-8	(2)
Grades 9-12	(3)

20. Current age of patient's female guardian *(mother, stepmother, or other) (show patient/guardian Flash Card #4; check only one):*

Not applicable (mother is deceased or patient has no stepmother or female guardian)	(0)
19 or younger	(1)
20-29 years	(2)
30-39 years	(3)
40-49 years	(4)
50-59 years	(5)
60 years or older	(6)

21. Highest educational level achieved by patient's female guardian *(mother, stepmother, or other) (show patient/guardian Flash Card #5; if education of female guardian is unknown, record as "n"; check only one):*

Never attended school	(0)
Did not complete high school	(1)
Completed high school	(2)
Some college or post high school education or training	(3)
Bachelor's degree or higher	(4)

22. Current age of patient's male guardian *(father, stepfather, or other) (show patient/guardian Flash Card #4; check only one):*

Not applicable (father is deceased or patient has no stepfather or male guardian)	(0)
19 or younger	(1)
20-29 years	(2)
30-39 years	(3)
40-49 years	(4)
50-59 years	(5)
60 years or older	(6)

23. Highest educational level achieved by patient's male guardian *(father, stepfather, or other) (show patient/guardian Flash Card #5; if education of male guardian is unknown, record as "n"; check only one):*

Never attended school	(0)
Did not complete high school	(1)
Completed high school	(2)
Some college or post high school education or training	(3)
Bachelor's degree or higher	(4)

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:

(Yes 1) (No 2)

30.

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

TONIC

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.

A. Center, patient 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: TONIC_3

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:

Yes (1) No (*2) STOP

** 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 (3)

C. Requirements for screening biopsy

10. Is this visit s1:

Yes (1) No (2) → **12.**

11. Is the date in item 9 within 6 months (183 days) of the anticipated date of randomization:

Yes (1) No (*2) Elig

** 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: (1)

b. Masson's trichrome stain: (1)

c. Iron stain: (1)

d. Other *(specify):* (1)

_____

e. Other *(specify):* (1)

_____

E. Unstained slides to be sent to the DCC

13. Are unstained slides available for sending to the DCC:

Yes (1) No (2)

16. ___

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)

c. 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)

16. Are any stained slides to be sent to the DCC:

Yes (1) No (2)

24. ___

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: ___ ___ (81-90)

b. Slide sequence number of Masson's trichrome stain: ___ ___ (81-90)

c. Slide sequence number of iron stain: ___ ___ (81-90)

d. Slide sequence number of other stain: ___ ___ (81-90)

19. Are any stained slides to be returned to the clinic:

Yes (1) No (2)

23. ___

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)

b. Slide sequence number: ___ ___ (81-90)

c. Slide sequence number: ___ ___ (81-90)

d. Slide sequence number: ___ ___ (81-90)

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 (2)

23. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department (1)

24.

Other, *(specify):* (2)

_____
name

_____
address

_____
address

_____
address

_____
phone

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.

G. Administrative information

24. Clinical Coordinator PIN: ____ ____ ____

25. Clinical Coordinator signature:

_____

26. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

Keyed: ( )

TONIC

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 patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of notification of intent to transfer:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____

6. Form & revision: t n 1

7. Study: TONIC 3

B. Last followup visit information

8. Date of last followup visit:

____ ____–____ ____ ____–____ ____
day mon year

9. Visit ID code of last completed followup visit:

f ____ ____ ____

10. Have cryovial and slide labels been sent to the adopting center:

Yes (1) No (*2)

** Send the cryovial and slide labels to the adopting center.*

C. Enrolling center administrative information

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

12. Clinical coordinator ID: ____ ____ ____

13. Clinical coordinator signature:

_____

D. Adopting center, patient and visit identification

14. Adopting center ID: ____ ____ ____ ____

15. Patient ID *(must be same as in Section A):*

____ ____ ____ ____

16. Patient code *(must be same as in Section A):*

____ ____ ____

17. Expected date of first followup visit at adopting center:

____ ____–____ ____ ____–____ ____
day mon year

18. Visit ID code for expected first followup visit at adopting center:

f ____ ____ ____

Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.

E. Adopting center administrative information

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

20. Clinical coordinator ID: ____ ____ ____

21. Clinical coordinator signature:

_____

Fax form to the DCC. The DCC will key the TN form.

NASH CRN Adult NAFLD Database 2

NASH CRN Pediatric NAFLD Database 2

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
IE	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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: **t 0** _____ _____

6. Form & revision: **a d 1**

7. Study: NAFLD Database 2 6

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient (1)
Interview with translator (2)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. 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 1-10 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
(0) → **21.**	(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?

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

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
(0)	(1)	(2)	(3)	(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
(0)	(1)	(2)	(3)	(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
(0)	(1)	(2)	(3)	(4)

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

No	Yes, but not in the last year	Yes, during the last year
(0)	(1)	(2)

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
(0)	(1)	(2)

21. Today's date:

_____

Thank you for completing this questionnaire.

NAFLD Database 2

BG - Baseline History

Purpose: To collect baseline history information about the patient.
When: Visit t0.
Administered by: Clinical Coordinator, reviewed by Study Physician.
Respondent: Patient or patient's parent.
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 NAFLD Database 2 Study. If ⊘EXC is checked for an item, the patient is ineligible and cannot enroll in the NAFLD Database 2 Study. 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.

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 0 ____ ____

6. Form & revision: b g 2

7. Study: NAFLD Database 2 6

B. Family history

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

(Yes 1) (No 2)

10.

a. Did any of the patient's first degree relatives die from liver disease:

(Yes 1) (No 2)

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

a. Alcohol related liver disease: (1)
b. Viral hepatitis: (1)
c. Alpha-1 antitrypsin deficiency: (1)
d. Wilson's disease: (1)
e. Glycogen storage disease: (1)
f. Iron overload: (1)
g. Fatty liver disease *(NAFLD, NASH):* (1)
h. Type of liver disease unknown: (1)
i. Other *(specify):* (1)

_____
specify

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

(Yes 1) (No 2)

12.

11. If yes, is the cause of the cirrhosis NASH-related or unknown (cryptogenic):

(Yes 1) (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)

14. Do any of the patient's first degree relatives (parent, brother, sister, child) have atrophy of body fat:

Yes (1)
No (2)
Don't know (3)

15. Do any of the patient's first degree relatives (parent, brother, sister, child) have a problem with cholesterol or blood fat:

Yes (1)
No (2)
Don't know (3)

C. NAFLD history

16. Date patient was first diagnosed with fatty liver disease or NASH-related cirrhosis:

____ ____–____ ____ ____–____ ____
day mon year

17. What prompted the evaluation for NAFLD, NASH, or NASH-related cirrhosis *(check all that apply)*

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)
e. Other *(specify):* (1)

_____
specify

18. What procedures/tests supported this first diagnosis *(check all that apply)*

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

_____
specify

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 evaluated for the Database 2 Study *(complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy):*

Yes (*1) No (2)
21.

**Blood drawn for specimen collection must be within 90 days of the biopsy.*

20. Date of liver biopsy no more than 90 days prior to registration in Database 2 Study that you want evaluated:

____ ____–____ ____ ____–____ ____
day mon year

21. Will the patient have a biopsy during screening:

Yes (*1) No (2)

**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 4 days after the biopsy.*

22. Has the patient had a liver imaging study in the past 6 months:

Yes (*1) No (2)

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

D. Weight history

23. What was the patient's birthweight:

____ ____–____ ____
lbs oz

24. *Review flashcard 11.* 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)
No or minimal change (6)

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

28. Is the patient age 18 or older:

Yes (1) No (2)
31.

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

____ ____ ____
lbs

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:

Yes (1) No (2)
33.

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

____ ____ ____
lbs

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

Yes (1) No (2)
35.

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:

Yes (1) No (2)
37.

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 12 or older:

Yes (1) No (2)
43.

38. Have you ever smoked tobacco cigarettes:

Never (1)
43.
In the past but not anymore (2)
Currently smokes cigarettes (3)

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):*

Yes (1) No (2)
43.

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

____ ____
years

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

____ ____
years

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

____ ____ ____
cigarettes/day

F. Menstrual history

43. Is the patient female:

(Yes 1) (No 2)

49.

44. Has menarche occurred:

(Yes 1) (No 2)

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:

(Yes 1) (No 2)

49.

48. 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 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: (1)

b. Diabetes type 2: (1)

c. Gestational diabetes *(diabetes of pregnancy):* (1)

d. Hepatitis B: (1) C

e. Hepatitis C: (1) C

f. Autoimmune hepatitis: (1)

g. Autoimmune cholestatic liver disorder (PBC or PSC): (1) C

h. Wilson's disease: (1) C

i. Alpha-1-antitrypsin (A1AT) deficiency: (1) C

j. Glycogen storage disease: (1) C

k. Iron overload: (1) C

l. Polycystic liver disease: (1)

m. Drug induced liver disease: (1)

n. Gilbert's syndrome: (1)

o. Esophageal or gastric varices on endoscopy: (1)

p. Bleeding from varices: (1)

q. Other gastrointestinal bleeding: (1)

r. Ascites: (1)

s. Edema: (1)

t. Hepatic encephalopathy: (1)

u. Portal hypertension: (1)

v. Hepatorenal syndrome: (1)

w. Hepatopulmonary syndrome: (1)

x. Short bowel syndrome: (1) C

y. Hemophilia *(bleeding disorder):* (1) C

z. HIV positive: (1) C

aa. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

ab. Endocrine disease *(hormonal abnormality):* (1)

ac. Hepatocellular carcinoma: (1) C

ad. Other malignancy *(cancer):* (1)

ae. Peripheral neuropathy: (1)

af. Seizure disorder or epilepsy: (1)

ag. Drug allergies: (1)

ah. Hypothyroidism: (1)

ai. Hypertension: (1)

aj. Cerebrovascular disease: (1)

ak. Dysbetalipoproteinemia: (1)

C

al. Chronic cholestasis: (1)

am. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

an. Pancreatitis: (1)

ao. Cholelithiasis: (1)

ap. Coronary artery disease: (1)

aq. Elevated uric acid such as gout: (1)

ar. Kidney disease: (1)

as. Polycystic ovary syndrome: (1)

at. Sleep apnea *(not breathing during sleep):* (1)

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (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 any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1)

C

b. Jejunoileal *(or other intestinal)* bypass prior to the diagnosis of NAFLD: (1)

C

c. Biliopancreatic diversion: (1)

C

d. Other GI or bariatric surgery *(specify):* (1)

_____

e. None of the above: (1)

51. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) No (2)

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

Yes (1) No (2)

52. Has the patient received total parenteral nutrition (TPN) for more than 1 month within 6 months prior to liver biopsy:

Yes (1) No (2)

F,Hg

53. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) No (2)

54. Does the patient have symptoms suggestive of sleep apnea *(snoring, observed periods of apnea, disruptive sleep disturbances):*

Yes (1) No (2)

H. Medication use

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

Yes (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, Glucotrol XL): (1)
f. Glyburide (Micronase, DiaBeta, Glynase): (1)
g. Insulin: (1)
h. Metformin (Glucophage, Glucophage XR): (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)

_____

56. Has the patient taken any alcohol abuse (dependance or withdrawal) medications in the past 3 months:

Yes (1) No (2) **57.**

(If 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)

_____

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

Yes (1) No (2) **58.**

(If yes, check all that apply):

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

_____

58. Has the patient taken any antiobesity medications in the past 3 months:

Yes (1) No (2) **59.**

(If yes, check all that apply):

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

_____

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

Yes (1) No (2) **60.**

(If yes, 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. Other, *(specify):* (1)

_____

j. Other, *(specify):* (1)

_____

60. Has the patient taken any strong opiates containing acetaminophen medication in the past 3 months:

Yes (1) No (2) **61.**

(If yes, check all that apply):

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

_____

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

Yes (1) No (2) **62.**

(If yes, 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)

_____

62. Has the patient taken any anticoagulant/antiplatelet medications in the past 3 months:

Yes (1) No (2) **63.**

(If yes, 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)

_____

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

( ) Yes ( ) No

64.

(If yes, check all that apply):

a. Betamethasone sodium (Celestone): ( )

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):* ( )

_____

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

( ) Yes ( ) No

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): ( )

l. Furosemide (Lasix): ( )

m. Hydrochlorothiazide (Esidrix, HydroDIURIL): ( )

n. Hydrochlorothiazide + triamterene (Dyazide): ( )

o. Lisinopril (Prinivil, Zestril): ( )

p. Losartan potassium (Cozaar): ( )

q. Losartan potassium with hydrochlorothiazide (Hyzaar): ( )

r. Metoprolol (Lopressor): ( )

s. Nifedipine (Adalat, Procardia): ( )

t. Perhexiline maleate: ( )

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):* ( )

_____

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

Yes (1) No (2)

66.

(If yes, check all that apply):

a. Conjugated estrogen (Premarin/Prempro): (1)

b. Diethylstilbestrol and methyltestosterone (Tylosterone): (1)

c. Esterified estrogen (Estratab, Menest): (1)

d. Estradiol (Estrace): (1)

e. Ethinyl estradiol (Estinyl): (1)

f. Fluoxymesterone (Android-F, Halotestin): (1)

g. Levonorgestrel (Norplant): (1)

h. Medroxyprogesterone (Cycrin, Provera): (1)

i. Megestrol (Megace): (1)

j. Methyltestosterone (Android): (1)

k. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): (1)

l. Norethindrone (Micronor): (1)

m. Norgestrel (Ovrette): (1)

n. Oral contraceptives: (1)

o. Oxandrolone (Oxandrin): (1)

p. Oxymetholone (Anadrol): (1)

q. Progesterone (Prometrium): (1)

r. Raloxifene (Evista): (1)

s. Tamoxifen (Nolvadex): (1)

t. Other, *(specify):* (1)

_____

u. Other, *(specify):* (1)

_____

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

Yes (1) No (2)

67.

(If yes, check all that apply):

a. Beclomethasone dipropionate (Beclovent, Vanceril): (1)

b. Budesonide (Pulmicort, Rhinocort): (1)

c. Fluticasone propionate (Flonase, Flovent): (1)

d. Loratadine (Claritin): (1)

e. Mometasone furoate (Nasonex): (1)

f. Triamcinolone acetonide (Azmacort, Nasacort): (1)

g. Other, *(specify):* (1)

_____

h. Other, *(specify):* (1)

_____

67. Has the patient taken a multivitamin regularly in the past 3 months:

Yes (1) No (2)

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

Yes (1) No (2)

70.

69. Which vitamins has the patient taken *(check all that apply):*

a. Vitamin B (any type): (1)

b. Vitamin C: (1)

c. Vitamin D: (1)

d. Vitamin E: (1)

e. Other, *(specify):* (1)

_____

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

Yes (1) No (2)

71.

(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): (1)
i. Cod liver oil: (1)
j. Coenzyme Q: (1)
k. Dichloroacetate: (1)
l. 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)

_____

ad. Other, *(specify):* (1)

_____

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

Yes (1) No (2)

72.

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

a. Demeclocycline (Declomycin): (1)
b. Divalproex (Depakote): (1)
c. Doxycycline (Monodox): (1)
d. Isotretinoin (Accutane): (1)
e. Levothyroxine (Levoxyl, Synthroid): (1)
f. Liothyronine (Cytomel): (1)
g. Methotrexate (Rheumatrex): (1)
h. Minocycline (Dynacin, Minocin): (1)
i. Oxytetracycline (Terramycin): (1)
j. Penicillamine (Cuprimine, Depen): (1)
k. Tetracycline (Achromycin): (1)
l. Trientine hydrochloride (Syprine): (1)
m. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)
n. Valproate sodium (Depacon): (1)
o. Valproic acid (Depakene): (1)
p. Other, *(specify):* (1)

_____

q. Other, *(specify):* (1)

_____

r. Other, *(specify):* (1)

_____

I. Administrative information

72. Study Physician PIN: ____ ____ ____

73. Study Physician signature:

_____

74. Clinical Coordinator PIN: ____ ____ ____

75. Clinical Coordinator signature:

_____

76. Date form reviewed:

____ ____–____ ____ ____–____ ____
day 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 **one** 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 **three** 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 **one** 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 **two** 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

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: b p 3

7. Study: NAFLD Database 2 6

B. Processing whole blood

Plasma and serum aliquots are to be separated from whole blood per instructions in the SOP I section. Draw fasting blood in the morning.

8. Was participant fasting for at least 8 hours* prior to blood draw:

Yes (1) No (2)

**12 hour fast is preferred.*

a. Was blood collected for the NIDDK Biosample Repository:

Yes (1)

Yes, collected for another study, but not used (2)

No, *(specify):* (* 3)

23. ____

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:

____ ____ : ____ ____ (1) (2)
hour minute am pm

10. Number of heparin (green-top) tubes: ____

11. Affix matching heparin tube MACO label *(only key NASH ID):*

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):*

NAFLD DB 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*

NAFLD DB 2 Serum 3*
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

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) (2)
hour minute am pm

b. Time of serum separation:

____ ____ : ____ ____ (1) (2)
hour minute am pm

16. Number of aliquots for plasma: ____ ____

17. Number of aliquots for serum: ____ ____

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

____ ____ : ____ ____ (1) (2)
hour minute am pm

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

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. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit :

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: t _____ _____ _____

6. Form & revision: b q 1

7. Study: NAFLD Database 2 6

C. Administrative information
(To be completed by clinical center staff after survey is completed.)

24. Clinical Coordinator PIN: ____ ____ ____

25. Clinical Coordinator signature:

_____

26. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

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: ___ ___ ___

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".

1) Indicate how often you drank the following beverages, for example, if you drank 5 glasses of water per week, circle response "3" under the column labeled "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 in cooking or other preparations, such as milk in cereal.

4) Count milk added to tea and coffee in the *tea/coffee with cream beverage category* **NOT** in the milk categories.

#		**a.**							**b.**				
		How often ***(circle 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.

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t____ ____ ____

6. Form & revision: c f 1

7. Study: NAFLD Database 2 6

B. Database 2 participation

8. This patient will continue in the NAFLD Database 2 study:

(Yes 1) (No 2)

10.

9. Has the patient or parent signed the latest version of the NAFLD Database 2 informed consent *(if applicable)*:

(Yes 1) (No * 2)

** Patient must sign the informed consent if required by local IRB*

C. Administrative information

10. Clinical Coordinator PIN: ____ ____ ____

11. Clinical Coordinator signature:

_____

12. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database 2

CG - Genetic Consent and Blood Collection Documentation

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 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/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 Repository.

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: c g 2

7. Study: NAFLD Database 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:

(Yes 1) (No 2)

10.

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

20.

10. Does the patient/parent consent to genetic research on NAFLD or NASH-related cirrhosis that is currently planned by the study investigators:

(Yes 1) (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:

(Yes 1) (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:

(Yes 1) (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 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/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):*

Yes (1) No (2)

20. ___

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)

16. ___

No, *(specify):* (2)

_____
specify

20. ___

16. Date and time of blood draw

a. Date:

___ ___–___ ___ ___–___ ___
day mon year

b. Time:

___ ___ : ___ ___ (1) am (2) pm
hour minute

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. 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

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit *(date form is initiated; effective date for suspension of visit completion)*:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: c o 1

7. Study: NAFLD Database 2 6

B. New study information

8. Study that patient has been or will be randomized in *(check only one)*:

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

C. Administrative information

10. Clinical Coordinator PIN: ____ ____ ____

11. Clinical Coordinator signature:

_____

12. 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

c r 3 6. Form and revision

__ 7. Study: **6**=Database 2

__ __ / __ __ __ / __ __ 8. Date of biopsy

B. Slide sequence number

9. 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 (*Specify*):

D. Histology

_____ *Patient ID*

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

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 (*does not require trichrome*); **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

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t ____ ____ ____

6. Form & revision: c v 1

7. Study: NAFLD Database 2 6

B. Framingham Risk Assessment

8. Was a lipid panel obtained at this visit:

Yes (1) No (2) → **21.**

9. Gender

Male (1)
Female (2)

10. Age: ____ ____ years

11. Are you a current cigarette smoker:

Yes (1) No (2)

12. Total cholesterol *(from LR form):*

____ ____ ____ mg/dL

If the patient has total cholesterol greater than 300 mg/dL, an IE form should be completed.

13. HDL cholesterol *(from LR form):*

____ ____ ____ mg/dL

14. LDL cholesterol *(from LR form)*:*

____ ____ ____ mg/dL

**Enter "GT" if LDL cannot be calculated due to high triglycerides.*

15. Blood pressure

a. Systolic blood pressure *(from PE form):*

____ ____ ____ mmHg

b. Diastolic blood pressure *(from PE form):*

____ ____ ____ mmHg

16. Are you currently being treated for high blood pressure with medicine prescribed by your doctor:

Yes (1) No (2)

17. Has anyone in your immediate family *(blood-related parent, brother, sister, or child)* been diagnosed with early heart disease *(before age 55 years for male relatives and before 65 years for female relatives):*

Yes (1) 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

b. Total cholesterol score
(based on items 10 and 12): ____ ____ points

c. Smoking score
(based on items 10 and 11): ____ points

d. HDL score *(based on item 13):* + / - ____ points

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 % ≥ 30, record ''30''.

C. ATP III guidelines

21. Have you been diagnosed with type 1 or type 2 diabetes:

Yes (1) No (2)

22. Have you been diagnosed with clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

Yes (1) No (2)

23.

(If yes, check all that apply)

a. Clinical CHD: (1)

b. Symptomatic carotid artery disease: (1)

c. Peripheral arterial disease: (1)

d. Abdominal aortic aneurysm: (1)

23. Was ''Yes'' checked for either item 21 or 22 or was LDL unknown (''GT'' in item 14 or lipid panel not obtained):

Yes (1) No (2)

25.

24. Is 10-year Framingham heart attack risk estimate 22% (item 20) or more:

Yes (1) No (2)

27.

25. Is LDL cholesterol (item 14) less than 100 mg/dL or was LDL unknown (''GT'' in item 14 or lipid panel not obtained):

Yes (1) No (2)

34.

26. Is LDL cholesterol (item 14) 130 mg/dL or more:

Yes (*1) No (†2)

34. **34.**

**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):* (1)

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):* (1)

e. Age in men ≥ 45 years or age in women ≥ 55 years *(based on items 9 and 10):* (1)

f. HDL cholesterol 60 mg/dL or more *(based on item 13):* (1)

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):

Yes (1) No (2)

32.

30. Is LDL cholesterol less than 130 mg/dL:

Yes (1) No (2)

34.

31. Is 10-year Framingham heart attack risk estimate between 10 and 20%, inclusive or LDL cholesterol 160 mg/dL or more:

Yes (*1) No (†2)

34. 34.

**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:

Yes (*1) No (2)

34.

**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 (†1) No (2)

†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: (1)

c. Stroke: (1)

d. Cerebrovascular disease: (1)

e. Coronary artery disease: (1)

f. Congestive heart failure: (1)

g. Peripheral vascular disease: (1)

h. Other cardiovascular disease *(specify):* (1)

_____
specify

i. None of the above: (1)

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

Men

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 Cholesterol	Points				
	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
3	1
4	1
5	2
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 _____%

Women

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 Cholesterol	Points				
	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

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 _____%

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: d r 2

7. Study: NAFLD Database 2 6

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Other caregiver: (1)
d. Health care provider or NASH CRN staff: (1)
e. Newspaper: (1)
f. Funeral parlor/home: (1)
g. Medical record: (1)
h. Medical examiner: (1)
i. Coroner: (1)
j. National Death Index (NDI): (1)
k. Social Security Death Master File (SSDMF): (1)
l. Other *(specify):* (1)

_____
other source

_____
other source

10. Place and location of death

a. Place of death *(check only one):*

Hospital (1)
Hospice (2)
Home (3)
Nursing home (4)
Other *(specify):* (5)

_____

Unknown (6)

b. Location of death:

_____
city/state/country

11. Has a death certificate been obtained:

Yes (1) No (2)

If no, please obtain or explain why not:

_____

_____

_____

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

Coronary heart disease (01) **13.**

Cardiovascular disease (02) **14.**

Liver disease (03) **15.**

Malignancy (cancer) (04) **16.**

Gastrointestinal (GI) disease (05) **17.**

Pulmonary (lung) disease (06) **18.**

Pneumonia (07) **19.**

Complication of diabetes (08) **19.**

Accident (09) **19.**

Suicide (10) **19.**

Homicide (11) **19.**

Kidney disease or renal failure (12) **19.**

Sepsis, staph or other infection (13) **19.**

Multi-organ failure (14) **19.**

Other *(specify):* (15) **19.**

_____

Unknown (16) **19.**

13. CAUSE OF DEATH: Coronary heart disease (CHD) subclassification ***(check only one)***:

Definite fatal myocardial infarction (MI) or heart attack (1)

Defined as:
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 (3)

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 (2)

Defined as: Death due to brady- or tachy- arrhythmias not associated with an acute ischemic event.

Cerebrovascular (stroke) (3)

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

Other cardiovascular (4)

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

Specify: _____

Go to 19.

15. CAUSE OF DEATH: Liver disease subclassification ***(check only one)***:

- Nonalcoholic fatty liver disease (NAFLD) (1)
- Chronic hepatitis C (2)
- Acute liver failure (3)
- Other *(specify):* (4)

_____

19. ___

16. CAUSE OF DEATH: Malignancy (cancer) subclassification ***(check only one)***:

- Breast cancer (01)
- Colon cancer (02)
- Endometrial/Uterine cancer (03)
- Esophageal cancer (04)
- Hepatocellular carcinoma (HCC)* (05)
  * *Complete and key the HC form.*
- Ovarian cancer (06)
- Pancreatic cancer (07)
- Prostate cancer (08)
- Rectal cancer (09)
- Other known cancer or malignant tumor *(specify):* (10)

_____

- Unknown cancer site (11)

19. ___

17. CAUSE OF DEATH: Gastrointestinal subclassification ***(check only one)***:

- Diverticular disease (1)
- *Clostridium difficile* colitis (2)
- Intestinal obstruction (3)
- Ulcer *(gastric, duodenal, peptic, gastrojejunal)* (4)
- Vascular disorders of the intestine (5)
- Other *(specify):* (6)

_____

19. ___

18. CAUSE OF DEATH: Pulmonary (lung) subclassification ***(check only one)***:

- Asthma (1)
- Acute respiratory failure (2)
- Interstitial lung disease (ILD) (3)
- Other *(specify):* (4)

_____

19. Contributing causes of death ***(check all that apply)***:

- **a.** Coronary heart disease (CHD) *(specify):* (1)

_____

- **b.** Cerebrovascular disease (stroke): (1)
- **c.** Congestive heart failure (CHF): (1)
- **d.** Documented arrhythmia, not associated with MI: (1)
- **e.** Other cardiovascular disease *(specify):* (1)

_____

- **f.** Diabetes Type 1: (1)
- **g.** Diabetes Type 2: (1)
- **h.** Liver disease *(specify):* (1)

_____

- **i.** Hepatocellular (liver) carcinoma (HCC)*: (1)
  * *Complete and key the HC form.*
- **j.** Other malignancy (cancer) *(specify):* (1)

_____

- **k.** Gastrointestinal (GI) disease *(specify):* (1)

_____

- **l.** Pulmonary (lung) disease *(specify):* (1)

_____

- **m.** Pneumonia: (1)
- **n.** Kidney disease: (1)
- **o.** Sepsis, staph or other infection: (1)
- **p.** Other *(specify):* (1)

_____

- **q.** Unknown: (1)
- **r.** None: (1)

20. Was this a procedure-related death:

Yes (1) No (2)

→ **22.**

21. Type of procedure-related death ***(check only one)***:

Cardiac death: Cardiovascular-related procedure
(Defined as death after invasive cardiovascular intervention. Death within 28 days of cardiovascular surgery or within 7 days of cardiac cath, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary vascular intervention.): (1)

Cardiac death: Noncardiovascular procedure
(Defined as cardiac death after noncardiovascular intervention which occurs within 28 days of surgery or other invasive procedure.): (2)

Non-cardiac death (3)

Unknown (4)

22. Was an autopsy performed ***(check only one)***:

Yes (1)

No (2)

Unknown (3)

23. Documentation available for future formal death adjudication ***(check all that 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 (1)

Narrative is not included (2)

If not, please explain why not:

_____

_____

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 year

Narrative - do not key:

NAFLD Database 2

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 (Elig) 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 STOP .

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: t 0 ____ ____

6. Form & revision: e n 1

7. Study: NAFLD Database 2 6

B. Current status

8. Was participant previously enrolled in a NASH CRN study:

Yes (1) No (2)

15. ⌐

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	(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	(7)

(Elig) ⌐

** 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:

Yes (1) No (2)

(Elig) ⌐

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:

Yes (1) → Elig; No (2)

b. Short bowel syndrome:

Yes (1) → Elig; No (2)

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)*:

Yes (1) → Elig; No (2)

d. History of biliopancreatic diversion:

Yes (1) → Elig; No (2)

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):* ____ 1-3

b. Serum total bilirubin subscore *(from Form LR: < 2.0 mg/dL=1, 2.0-3.0=2, > 3.0=3):* ____ 1-3

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

f. Child-Pugh Turcotte score *(sum items 12a + 12b + 12c + 12d + 12e):*

____ ____ 5-15

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

Yes (1) → Elig; No (2)

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):*

( ) Yes (1) ( ) No (2)
→ Elig

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

( ) Yes (1) ( ) No (2)
→ Elig

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

( ) Yes (1) ( ) No (2)
→ Elig

d. Wilson's disease:

( ) Yes (1) ( ) No (2)
→ Elig

e. Known glycogen storage disease:

( ) Yes (1) ( ) No (2)
→ Elig

f. Known dysbetalipoproteinemia:

( ) Yes (1) ( ) No (2)
→ Elig

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

( ) Yes (1) ( ) No (2)
→ Elig

h. Congenital hepatic fibrosis or polycystic liver disease:

( ) Yes (1) ( ) No (2)
→ Elig

i. Other metabolic/congenital liver disease:

( ) Yes (1) ( ) No (2)
→ Elig

j. HIV infection or other systemic infectious disease:

( ) Yes (1) ( ) No (2)
→ Elig

k. Disseminated or advanced extrahepatic malignancy:

( ) Yes (1) ( ) No (2)
→ Elig

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

( ) Yes (1) ( ) No (2)
→ Elig

14. Do any of the patient's assessments show evidence of these histologic exclusions

a. Hepatic iron index > 1.9:

Yes (1) No (2) → Elig

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

Yes (1) No (2) → Elig

c. Chronic cholestasis:

Yes (1) No (2) → Elig

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

Yes (1) No (2) → Elig

e. Iron overload greater than 3+:

Yes (1) No (2) → Elig

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

Yes (1) No (2) → Elig

g. Multiple epithelioid granulomas:

Yes (1) No (2) → Elig

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:

Yes (1) No (2) → Elig

E. Check on plasma and serum collection and histologic criteria for inclusion in Database 2 study

16. Date of plasma and serum collection:

____ ____–____ ____ ____–____ ____
day mon year

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:

Yes (1)
No (2) → **19.**

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)* (2)

Participant was previously enrolled in a NASH CRN study, but has not had a biopsy within past 3 months (3)

None of the above (4) → Elig

G. Eligibility check

20. Was an ineligibility condition checked or an eligibility not ascertained in items 9-15 or item 19:

Yes (1) No (2)

→ **23.**

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:

Yes (1) → **23.**

No (2)

Task not run because patient is known to be ineligible (*3) → **23.**

**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):*

Yes (*1) → **24.** No (2) → **Elig**

**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: (1)

b. Tests are outside time window and clinic chose not to repeat tests: (1)

c. Other reason not covered on this form *(specify):* (1)

_____

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

NAFLD Database 2

FR - FibroScan® Report

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 FibroScan® exam):*

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: f r 5

7. Study: NAFLD Database 2 6

B. Consent

8. Has the patient signed the FibroScan® consent:

Yes (1) No (*2)

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.: (1)

b. Wound near the site of scan: (1)

c. Pregnancy: (1)

d. Ascites (fluid in the abdomen): (1)

e. Patient did not fast for 3 hours: (1)

f. Were any of the items above (a-e) checked:

Yes (*1) No (2)

21. ____

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

C. FibroScan® Procedure information

10. Was FibroScan® exam performed:

Yes (1) No (* 2)

12.

** Complete item 11, then skip to item 21.*

11. Reason FibroScan® exam not performed *(check all that apply):*

a. Patient had a skin-to-capsule distance measurement greater than 3.5cm: (1)

b. Other *(specify):* (1)

_____

Skip to item 21.

12. Probe type used:

M: (1)

XL: (2)

D. FibroScan® exam #1 results

13. FibroScan® Technician PIN: ____ ____ ____

14. Number of measurements

a. Valid measurements*: ____ ____ # of valid measurements

b. Invalid measurements: ____ ____ # of invalid measurements

c. Total measurements: ____ ____ # of total measurements

To calculate invalid measurements, subtract valid measurements from total measurements

** Note: at least ten valid measurements should be made.*

15. Equivalent Liver Stiffness (E)

a. Median (kPa): ____ ____ ____ • ____ (1.5-75.0)

b. IQR (kPa): ____ ____ ____ • ____

c. IQR/med: ____ ____ %

16. Controlled Attenuation Parameter (CAP)

a. Median (dB/m): ____ ____ ____ (100-400)

b. IQR (dB/m): ____ ____ ____

E. FibroScan® exam #2 results

(This may be done by the same technician or a different technician).

17. FibroScan® Technician PIN: ____ ____ ____

18. Number of measurements

a. Valid measurements*: ____ ____ # of valid measurements

b. Invalid measurements: ____ ____ # of invalid measurements

c. Total measurements: ____ ____ # of total measurements

To calculate invalid measurements, subtract valid measurements from total measurements

** Note: at least ten valid measurements should be made.*

19. Equivalent Liver Stiffness (E)

a. Median (kPa): ____ ____ ____ • ____ (1.5-75.0)

b. IQR (kPa): ____ ____ ____ • ____

c. IQR/med: ____ ____ %

20. Controlled Attenuation Parameter (CAP)

a. Median (dB/m): ____ ____ ____ (100-400)

b. IQR (dB/m): ____ ____ ____

F. Administrative information

21. Study Physician PIN: ____ ____ ____

22. Study Physician signature:

_____

23. Clinical Coordinator PIN: ____ ____ ____

24. Clinical Coordinator signature:

_____

25. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

Keyed: ( )

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: n ____ ____ ____

6. Form & revision: h c 1

7. Study: NAFLD Database 2 6

B. Diagnosis information

8. Date of diagnosis:

____ ____–____ ____ ____–____ ____
day mon year

9. How was HCC identified *(check all that apply):*

a. Ultrasound: (1)
b. CT scan: (1)
c. MRI: (1)
d. Biopsy: (1)
e. Other *(specify):* (1)

_____

10. Were results of imaging obtained:

Yes (1) No (2)
15.

11. Were multiple tumors identified:

Yes (1) No (2)

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

____ ____ . ____
cm

13. Was early enhancement present:

Yes (1) No (2)

14. Was delayed washout present:

Yes (1) No (2)

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

Yes (1) No (2)
16.

a. Was serum AFP elevated: Yes (1) No (2)

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:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database 2 — 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t 0 ____ ____

6. Form & revision: h f 2

7. Study: NAFLD Database 2 6

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

a. Biopsy length: ____ ____ mm

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)

b. Masson's trichrome: (1)

C. NAFLD evaluation (use H & E and Masson's trichrome slides only)

10. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5%	(0)
5-33%	(1)
34-66%	(2)
> 66%	(3)

b. Location:

Zone 3	(0)
Zone 1	(1)
Azonal	(2)
Panacinar	(3)

11. Fibrosis stage *(Masson's trichrome stain)*

0: None	(0)
1a: Zone 3, perisinusoidal (requires trichome)	(1)
1b: Zone 3, perisinusoidal (easily seen on H&E)	(2)
1c: Portal/periportal only	(3)
2: Zone 3 and periportal, any combination	(4)
3: Bridging	(5)
4: Cirrhosis	(6)

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)
> 4 / 20x mag (3)

b. Amount of portal, chronic inflammation:

None to minimal (0)
Mild (1)
More than mild (2)

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) (2)
Suspicious/borderline/indeterminate, zone 1, periportal pattern (1B) (3)
Yes, definite steatohepatitis (4)

D. Exclusion of other liver disease

15. Is there evidence of primary biliary cirrhosis:

(Yes 1) (No 2)

16. Is there evidence of Wilson's disease:

(Yes * 1) (No 2)

C

** 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)
b. Florid duct lesions: (* 1)
c. Cholate stasis: (1)
d. Copper deposition: (1)
e. Other *(specify):* (1)

_____

f. None: (1)

** Caution: Exclusionary if the study physician agrees with diagnosis.*

18. Features of other forms of chronic liver disease *(check all that apply):*

a. Vascular lesions of ALD/B-C/OVD: (1)
b. Inflammation suggestive of AIH, HCV: (* 1)
c. Pigment suggestive of HH: (1)
d. Globules suggestive of A1AT: (* 1)
e. Hepatocellular changes suggestive of HBV: (* 1)
f. Granulomas suggestive of sarcoid, PBC, infection: (* 1)
g. Other *(specify):* (1)

_____

h. None: (1)

** Caution: Exclusionary if the study physician agrees with diagnosis.*

E. Evaluation of cryptogenic cirrhosis

19. Is cirrhosis present:

(Yes 1) (No 2)

22.

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):*

(Yes 1) (No 2)

22.

21. Other features *(check all that apply):*

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 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

NAFLD Database 2

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:

(* Yes 1) (No 2)

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

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

(* Yes 1) (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:

(Yes 1) (No 2)

19. ____

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

Never (0)

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 (4)

14. 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)

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)

E. Tobacco cigarette smoking

16. Since the last visit, have you smoked tobacco cigarettes regularly *("No" means smoked less than 1 day per week on average):*

Yes (1) No (2)

19. ____

17. On average, how many days per week have you smoked cigarettes: ____ # days

18. On the days that you smoked, about how many cigarettes did you smoke per day:

____ ____ ____ # cigarettes per day

F. Medical history

19. 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)*

a. Diabetes type 1: (1)
b. Diabetes type 2: (1)
c. Gestational diabetes *(diabetes of pregnancy):* (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)
l. Gilbert's syndrome: (1)
m. Esophageal or gastric varices on endoscopy: (1)
n. Bleeding from varices: (1)
o. Other gastrointestinal bleeding: (1)
p. Ascites: (1)
q. Edema: (1)
r. Hepatic encephalopathy: (1)
s. Portal hypertension: (1)
t. Hepatorenal syndrome: (1)
u. Hepatopulmonary syndrome: (1)
v. Short bowel syndrome: (1)
w. Hemophilia *(bleeding disorder):* (1)
x. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)
y. Endocrine disease *(hormonal abnormality):* (1)
z. Hepatocellular carcinoma: (1)
aa. Other malignancy *(cancer):* (1)
ab. Peripheral neuropathy: (1)
ac. Seizure disorder or epilepsy: (1)
ad. Drug allergies: (1)
ae. Hypothyroidism: (1)
af. Hypertension: (1)
ag. Cerebrovascular disease: (1)
ah. Dysbetalipoproteinemia: (1)
ai. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)
aj. Pancreatitis: (1)
ak. Cholelithiasis: (1)
al. Coronary artery disease: (1)
am. Elevated uric acid such as gout: (1)
an. Kidney disease: (1)
ao. Polycystic ovary syndrome: (1)
ap. Sleep apnea *(not breathing during sleep):* (1)
aq. Dermatologic disorders: (1)
ar. Myopathy: (1)
as. Myositis: (1)
at. Major depression: (1)
au. Schizophrenia: (1)
av. Bipolar disorder: (1)
aw. Obsessive compulsive disorder: (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)*

a. Stapling or banding of the stomach: (1)
b. Jejunoileal *(or other intestinal)* bypass: (1)
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 (1) No (2)

22. Since the last visit, has the patient received total parenteral nutrition (TPN):

Yes (1) No (2)

23. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) No (2)

24. Since the last visit, has the patient been hospitalized:

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 (2)
26.

If Yes, specify:

_____
specify

G. Medication use

26. Since the last visit, has the patient used any antidiabetic medications *(If yes, check all that apply)*

Yes (1) No (2)
27.

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): (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)

_____

27. Since the last visit, has the patient taken any alcohol abuse (dependance or withdrawal) medications:

Yes (1) No (2)

28. Since the last visit, has the patient taken any antihyperlipidemic medications *(If yes, check all that apply)*

	Yes (1)	No (2)
	29.	
a. Atorvastatin (Lipitor):	(1)	
b. Colestipol hydrochloride (Colestid):	(1)	
c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate):	(1)	
d. Gemfibrozil (Gen-Fibro, Lopid):	(1)	
e. Fenofibrate (Tricor):	(1)	
f. Fluvastatin sodium (Lescol):	(1)	
g. Lovastatin (Mevacor):	(1)	
h. Nicotinic acid (Niaspan):	(1)	
i. Pravastatin sodium (Pravachol):	(1)	
j. Rosuvastatin (Crestor):	(1)	
k. Simvastatin (Zocor):	(1)	
l. Other, *(specify):*	(1)	

_____

29. Since the last visit, has the patient taken any antiobesity medications:

Yes (1) No (2)

30. Since the last visit, has the patient taken any systemic corticosteroids:

Yes (1) No (2)

31. Since the last visit, has the patient taken any cardiovascular/antihypertensive medications *(If yes, check all that apply)*

	Yes (1)	No (2)
	32.	
a. Amiodarone (Pacerone):	(1)	
b. Amlodipine besylate (Norvasc):	(1)	
c. Atenolol (Tenormin):	(1)	
d. Benazepril (Lotensin):	(1)	
e. Captopril (Capoten):	(1)	
f. Clonidine (Catapres):	(1)	
g. Digoxin (Lanoxin):	(1)	
h. Diltiazem (Cardizem):	(1)	
i. Doxazosin (Cardura):	(1)	
j. Enalapril (Vasotec):	(1)	
k. Felodipine (Plendil):	(1)	
l. Furosemide (Lasix):	(1)	
m. Hydrochlorothiazide (Esidrix, HydroDIURIL):	(1)	
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):	(1)	
s. Nifedipine (Adalat, Procardia):	(1)	
t. Perhexiline maleate:	(1)	
u. Propranolol (Inderal):	(1)	
v. Quinapril (Accupril):	(1)	
w. Terazosin (Hytrin):	(1)	
x. Timolol maleate (Blocadren):	(1)	
y. Valsartan (Diovan):	(1)	
z. Verapamil (Calan):	(1)	
aa. Other, *(specify):*	(1)	

_____

ab. Other, *(specify):* (1)

_____

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 (1)	No (2)
a. Oral contraceptives:	(1)	
b. Raloxifene (Evista):	(1)	
c. Tamoxifen (Nolvadex):	(1)	
d. Other, *(specify):*	(1)	

33.

_____

33. Since the last visit, has patient taken any of the following vitamins or supplements *(If yes, check all that apply)*

	Yes (1)	No (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:	(1)	
o. Echinacea:	(1)	
p. Fish oil (any form):	(1)	
q. Flax seed oil:	(1)	
r. Garlic:	(1)	
s. Ginkgo biloba:	(1)	
t. Glucosamine (any form):	(1)	
u. Lecithin:	(1)	
v. Milk thistle:	(1)	
w. N-acetyl-cysteine:	(1)	
x. S-adenylmethionine (SAM-e):	(1)	
y. Saw palmetto:	(1)	
z. Selenium:	(1)	
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)*

	Yes (1)	No (2)
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):	( )	
k. Ursodeoxycholic acid (Actigall, Urso, Ursodiol):	( )	
l. Valproate sodium (Depacon):	( )	
m. Valproic acid (Depakene):	( )	
n. Other, *(specify):*	( )	
_____		
o. Other, *(specify):*	( )	
_____		

35. Since the last visit, has patient taken any pain relieving, non-steroidal anti-inflammatory, aspirin, or acetaminophen-containing medications:

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

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	( ) 3

I. Administrative information

37. Study Physician PIN: ____ ____ ____

38. Study Physician signature:

_____

39. Clinical Coordinator PIN: ____ ____ ____

40. Clinical Coordinator signature:

_____

41. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code:

n ____ ____ ____

6. Form & revision: i e 3

7. Study: NAFLD Database 2 6

B. Visit interval identification

8. Most recently completed visit (screening or follow-up)

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____ ____

C. Patient information

9. Date enrolled in NAFLD Database 2 Study *(enter n if patient is not yet enrolled):*

____ ____–____ ____ ____–____ ____
day mon year

10. Gender:

Male (1)
Female (2)

11. Age at time of event: ____ ____
years

D. Event description

12. Date event started:

____ ____–____ ____ ____–____ ____
day mon year

13. Nature of event *(check all that apply)*

a. General anesthesia (1)
b. Study-related procedure: (1)
c. Drug interactions: (1)
d. Worsening of a co-morbid illness: (1)
e. Hypoglycemia: (1)
f. New-onset diabetes: (1)
g. Pregnancy *(patient):* (1)
h. Cirrhosis: (1)
i. Hepatocellular carcinoma (HCC): (* 1)
** Complete and key the HC form.*
j. Other *(specify):* (1)

_____

_____

14. Did the event lead to *(check all that apply)*

a. Emergency room visit: (1)

b. Hospitalization: (1)

c. Infectious episode: (1)

d. Surgical intervention: (1)

15. Describe event:

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*):

Yes (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):

17. Indicate the severity code using the CTCAE grading scale for the AE specified (*severity grades are listed in the CTCAE v3.0 document available at https://jhuccs1.us/nash/default.asp; click on Documents and then click on General Documents*):

Grade 1 - Mild (1)

Grade 2 - Moderate (2)

Grade 3 - Severe† (3)

Grade 4 - Life threatening or disabling† (4)

Grade 5 - Death† (* 5)

†*Fax the DCC (Attention Pat Belt) a copy of this form if severity grade is 3 or higher (Fax 410-955-0932).*

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

18. Date event resolved
(enter n if event is not yet resolved):

____ ____–____ ____ ____–____ ____
day mon year

19. What action was taken:

20. Other comments on event:

F. Administrative information

21. Clinical Coordinator PIN: ____ ____ ____

22. Clinical Coordinator signature:

23. Study Physician PIN: ____ ____ ____

24. Study Physician signature:

25. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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.

NAFLD Database 2

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: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: i r 1

7. Study: NAFLD Database 2 6

B. Upper abdominal ultrasound

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

Yes (1) No (2)

11.

9. Date of most recent upper abdominal ultrasound:

____ ____–____ ____ ____–____ ____
day mon year

10. 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. Intrahepatic biliary dilatation: (1)
f. Extrahepatic biliary dilatation: (1)
g. Gallstones/cholelithiasis: (1)
h. Gall bladder polyps: (1)
i. Cholecystectomy: (1)
j. Splenomegaly: (1)
k. Ascites: (1)
l. Other features of portal hypertension *(specify):* (1)

_____

_____

m. Other abnormality *(specify):* (1)

_____

_____

n. None of the above: (1)

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)*:

(Yes 1) (No 2)

14.

12. Date of most recent upper abdominal CT scan:

____ ____–____ ____ ____–____ ____
day mon year

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

_____

_____

o. Other abnormality *(specify):* (1)

_____

_____

p. None of the above: (1)

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)*:

(Yes 1) (No 2)

17.

15. Date of most recent upper abdominal MRI:

____ ____–____ ____ ____–____ ____
day mon year

16. 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. Splenomegaly: (1)
j. Ascites: (1)
k. Other features of portal hypertension *(specify):* (1)

_____

_____

l. Other abnormality *(specify):* (1)

_____

_____

m. None of the above: (1)

E. Administrative information

17. Study Physician PIN: ____ ____ ____

18. Study Physician signature:

_____

19. Clinical Coordinator PIN: ____ ____ ____

20. Clinical Coordinator signature:

_____

21. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database 2

LD – Lifetime Drinking History (Skinner)

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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____ _____

6. Form & revision: **l d 1**

7. Study: NAFLD Database 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):

Yes (1) No (2)

81. ◄

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)*	(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)*:

		Positive	Negative	Neutral
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)

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 _____ _____ _____ %

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 ____ ____ ____ %

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":

Yes (1) No (2)

81. ◄

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:

Yes (1) No (2)

30. ◄

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)*:

	Positive	Negative	Neutral
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)

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 ____ ____ ____ %

With others ____ ____ ____ %

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 be "000")*:

Morning ____ ____ ____ %

Afternoon ____ ____ ____ %

Evening ____ ____ ____ %

E. Next 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 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 (1) No (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:

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")*:

Beer ____ ____ ____ %

Liquor ____ ____ ____ %

Wine ____ ____ ____ %

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)

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

Yes (1) No (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)*:

		Positive	Negative	Neutral
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":

Yes (1) No (2)

→ **81.**

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

a. Years: ____ ____ yrs

b. Months: ____ ____ mos

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:

____ ____ # drinks

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

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 (1) No (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)*:

		Positive	Negative	Neutral
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"*:

Yes (1) No (2)

81. ◀

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

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

____ ____
drinks

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

____ ____
days

61. 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.*)

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 ____ ____ ____
%

Liquor ____ ____ ____
%

Wine ____ ____ ____
%

63. 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)

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

Yes (1) No (2)

66. ◄

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 effect)*:

	Positive	Negative	Neutral
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)

66. 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 ____ ____ ____
%

67. 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 ____ ____ ____
%

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 (1) No (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.*)

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 ____ ____ % ____

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)

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

Yes (1) No (2)

→ **78.**

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)*:

		Positive	Negative	Neutral
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)

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 all 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 ____ ____ ____ %

Evening ____ ____ ____ %

I. Number of phases

80. Are there any additional subsequent phases:

Yes (* 1) No (2)

***** *If yes, complete a second LD form.*
Skip sections B and C on second form.

J. Administrative information

81. Clinical Coordinator PIN: ____ ____ ____

82. Clinical Coordinator signature:

_____

83. Date form reviewed:

____ ____-____ ____ ____-____ ____
day mon year

NAFLD Database 2

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit *(date form was initiated):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t ____ ____ ____

6. Form & revision: l r 3

7. Study: NAFLD Database 2 6

B. Hematology

8. Date of blood draw for complete blood count:

____ ____–____ ____ ____–____ ____
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).

9. Hemoglobin: ____ ____ • ____
g/dL

10. Hematocrit: ____ ____ • ____
%

11. Mean corpuscular volume (MCV):

____ ____ ____
fL

12. Blood cell count

a. White blood cell count (WBC):

____ ____ ____ • ____ ____
10^3 cells/μL or 10^9 cells/L

b. Red blood cell count (RBC):

____ ____ • ____ ____
mill cells/μL

13. Platelet count:

____,___ ____ ____,___ ____ ____
cells/μL

C. Chemistries and HbA1c

14. Date of blood draw for chemistries:

____ ____–____ ____ ____–____ ____
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).

15. Blood urea nitrogen (BUN): ____ ____
mg/dL

16. Creatinine: ____ ____ • ____
mg/dL

17. Uric acid: ____ ____ • ____
mg/dL

18. Date of blood draw for HbA1c:

____ ____–____ ____ ____–____ ____
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): ____ ____ • ____ ____ mg/dL

22. Bilirubin (direct): ____ ____ • ____ ____ mg/dL

23. Aspartate aminotransferase (AST)

____ ____ ____ U/L

a. Upper limit of normal: ____ ____ U/L

24. Alanine aminotransferase (ALT)

____ ____ ____ U/L

a. Upper limit of normal: ____ ____ U/L

25. Alkaline phosphatase ____ ____ ____ ____ U/L

a. Upper limit of normal: ____ ____ ____ U/L

26. Gamma glutamyl transferase (GGT):

____ ____ ____ ____ U/L

27. Total protein: ____ ____ • ____ g/dL

28. Albumin: ____ • ____ g/dL

29. Prothrombin time (PT): ____ ____ • ____ sec

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:

Yes (1) No (*2)

**12 hour fasting is preferred, but will accept non-fasting 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

b. Total cholesterol: ____ ____ ____ mg/dL

c. HDL cholesterol: ____ ____ ____ mg/dL

d. LDL cholesterol*: ____ ____ ____ 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:

Yes (1) No (*2)

35.

**Patient must be fasting; 12 hour fast is preferred.*

34. Date of blood draw for fasting glucose and insulin levels:

____ ____–____ ____ ____–____ ____
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). The serum glucose and insulin value should be obtained from the same blood draw.

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ ____ • ____ ____
μU/mL

G. 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

NAFLD Database 2

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.

Continuing Database 2 patients: 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 EHG 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t 0 ____ ____

6. Form & revision: 1 s 2

7. Study: NAFLD Database 2 6

8. Is the patient a continuing participant from Database, PIVENS, or TONIC:

(Yes 1) (No *2)

10. ____

**All laboratory test results are required during screening.*

9. Are new laboratory results available for the continuing participant:

(Yes *1) (No 2)

39. ____

**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 (1) EHG ____
Negative (2)

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 (1)
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 (1) EHG ____
Negative (2)

e. Hepatitis C virus RNA:

Positive	(1)
Negative	(2)
Not available	(3)

f. Hepatitis A virus antibody *(anti-HAV, total):*

Positive	(1)
Negative	(2)
Not available	(3)

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

b. Total iron binding capacity: ____ ____ ____ µg/dL

c. Ferritin:

____ ____ ____ ____ ng/mL

12. Is hepatic iron index available:

Yes (1) No (2)

14.

13. Hepatic iron index: ____ ____ ____ µMol/g/year

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+:

Yes (1) No (2)

17.

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:

Yes (1) No (2)

18.

a. Is a ceruloplasmin value available:

Yes (1) No (2)

20.

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):*

____ ____–____ ____ ____–____ ____
day mon year

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

19. Ceruloplasmin ____ ____ • ____ mg/dL

a. Upper limit of normal: ____ ____ • ____ mg/dL

b. Lower limit of normal: ____ ____ • ____ mg/dL

F. Alpha-1 antitrypsin

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

____ ____–____ ____ ____–____ ____
day mon year

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

21. Alpha-1 antitrypsin (A1AT) ____ ____ ____ mg/dL

a. Upper limit of normal: ____ ____ ____ mg/dL

b. Lower limit of normal: ____ ____ ____ mg/dL

22. A1AT phenotype:

a. Pi Z heterozygote:

Yes (1)
No (2)
Unknown (3)

b. Pi ZZ homozygote:

Yes (1)
No (2)
Unknown (3)

23. A1AT deficiency *(physician judgment):*

Yes (1) No (2)
F.Hg

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 (2)
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)
27.

**If positive ASMA value, complete either a or b depending on laboratory results:*

a. Titer *(record only the denominator):*

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____

27. Antimitochondrial antibody (AMA):

Positive (*1)
Negative (2)
28.
Age < 18 and not done (3)
28.

**If positive AMA value, complete either a or b depending on laboratory results:*

a. Titer *(record only the denominator):*

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____

28. Is patient 18 or older:

Yes (1) No (2)
32.

29. Lymphocytotoxic antibody (LCA):

Positive (*1)
Negative (2)
30.
Not available (3)
30.

**If positive LCA value, complete either a or b depending on laboratory results:*

a. Titer *(record only the denominator):*

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____

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

Positive (*1)
Negative (2)
31.
Not available (3)
31.

**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)
32.
Not available (3)
32.

**If positive, record RF value.*

a. Units: ___ ___ • ___
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:

Yes (1) No (2)
37.

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

NAFLD Database 2

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 t0, t048, t096, 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 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____ ____

6. Form & revision: 1 t 2

7. Study: NAFLD Database 2 6

B. Liver biopsy/RNA*later*® Solution storage procedures

8. Date of biopsy:

____ ____–____ ____ ____–____ ____
day mon year

9. Was the liver tissue obtained from a needle core biopsy *(as opposed to a wedge biopsy):*

Yes (1) No (2)

10. Was liver tissue placed in RNA*later*® Solution preferably within 1 minute, but no more than 5 minutes after biopsy:

Yes (1) No (*2)

13. ____

* *Discard liver tissue*

11. Was liver tissue refrigerated at 4° C overnight, then transferred to freezer for storage:

Yes (1) No (2)

12. ____

a. If no, describe conditions of local storage:

_____

_____

C. Cryovial label

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):*

D. Administrative information

13. Clinical Coordinator PIN: ____ ____ ____

14. Clinical Coordinator signature:

_____

15. Date form reviewed:

____ ____–____ ____ ____–____ ____
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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit: ____ ____ – ____ ____ – ____ ____
day mon year

5. Visit code: t ____ ____ ____

6. Form & revision: m v 1

7. Study: NAFLD Database 2 6

B. Reason for completion of this form

8. Was the entire visit missed:

Yes (1) No (2)

11.

C. Missed visit information

9. Reason for missed visit *(check all that apply)*

a. Patient was ill: (1)

b. Patient was temporarily away from area: (1)

c. Patient refused to return: (1)

d. Patient has permanently moved from the area: (1)

e. Unable to contact patient: (1)

f. Other *(specify):* (1)

_____
specify

10. Steps taken to avoid missing the visit *(check all that apply)*

a. Telephoned patient: (1)

b. Mailed reminder card: (1)

c. Other *(specify):* (1)

_____
specify

14.

D. Missed form information

11. Check form(s) not completed *(check required forms that were missed)*

a. Blood Processing for Plasma and Serum (BP): (1)

b. Followup Medical History (HI): (1)

c. Laboratory Results - Tests Done During Screening and Followup (LR): (1)

d. Physical Examination (PE): (1)

e. 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. 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t ____ ____ ____

6. Form & revision: p e 1

7. Study: NAFLD Database 2 6

B. Measurements

8. Height *(shoes off - repeat height measurements until you have two measurements within 0.5 inches (1.3 cm) of each other):*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off - repeat weight measurements until you have two measurements within 2 lbs (0.91 kg) of each other):*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

10. Waist *(standing, at midpoint between highest point of iliac crest and lowest point of costal margin; repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

11. Hip *(standing, at fullest part of the hips; repeat hip measurements until you have two measurements within 4 inches (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral or other as appropriate for age):*

a. Degrees: ___ ___ ___ • ___

b. Scale:

Fahrenheit: (1)

Centigrade: (2)

13. Blood pressure

a. Systolic: ___ ___ ___ mmHg

b. Diastolic: ___ ___ ___ mmHg

14. Resting radial pulse: ___ ___ ___ beats/minute

15. Respiratory rate: ___ ___ breaths/minute

C. Examination findings

16. Areas with acanthosis nigricans *(check all that apply):*

a. None: (1)

b. Neck: (1)

c. Axilla: (1)

d. Elbows: (1)

e. Knees: (1)

f. Knuckles: (1)

g. Periumbilical: (1)

17. Abdomen abnormalities present *(check all that apply):*

a. None: (1)

b. Ascites: (1)

c. Obese: (1)

d. Splenomegaly: (1)

e. Hepatomegaly: (1)

If Yes, span at right midclavicular line:

___ ___ • ___ cm

D. Liver signs

18. Focused liver signs *(check all that apply)*

a. None: (1)

b. Jaundice: (1)

c. Palmar erythema: (1)

d. Contractures: (1)

e. Pedal edema: (1)

f. Spider angiomata: (1)

g. Asterixis: (1)

h. Hepatic encephalopathy: (1)

i. Other, *(specify):* (1)

_____ specify

E. Tanner Staging

19. Is Tanner staging required for this patient *(Note: Required during screening if patient is 17 years old or younger.) (check only one):*

Yes, patient has not reached full sexual maturity and is 17 years old or younger: (1)

No, patient is 18 years old or older (2)

27.

No, participant had reached full sexual maturity *(Tanner stage 5 on all parameters at screening or for 2 consecutive visits)* (3)

27.

20. Is the patient female:

Yes (1) No (2)

23.

Male Tanner Staging

21. Genital stage: ___ 1-5

22. Pubic hair stage: ___ 1-5

27.

Female Tanner Staging

23. Breast stage: ____ (1-5)

24. Pubic hair stage: ____ (1-5)

25. Has menarche occurred:

(Yes 1) (No 2)

27.

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

____ ____ age in years

F. Administrative information

27. Study Physician PIN: ____ ____ ____

28. Study Physician signature:

_____

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: t 0 ____ ____

6. Form & revision: r c 1

7. Study: NAFLD Database 2 6

B. NAFLD Database participation

8. Date in item 4 of original Database RG form: ____ ____–____ ____ ____–____ ____
day mon year

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature: _____

11. Date form reviewed: ____ ____–____ ____ ____–____ ____
day mon year

NAFLD Database 2

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.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: t 0 ____ ____

6. Form & revision: r g 1

7. Study: NAFLD Database 2 6

B. Consent

8. Has the patient (or patient's guardian) signed the NAFLD Database 2 informed consent statement:

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

STOP

C. Information about patient

9. Date of birth:

____ ____ – ____ ____ ____ – ____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

10. Age at last birthday: ____ ____
years

11. Gender:

Male (1)
Female (2)

12. Ethnic category *(show the patient/parent 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)

14.

13. What describes your Hispanic, Latino, or Latina origin best *(show the patient/parent Flash Card #1 and ask the respondent 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

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)*

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 *(check only one):*

Continental US (includes Alaska) or Hawaii (1)
Other, *(specify):* (2)

_____
specify

16. Highest educational level achieved by patient *(show the patient/parent Flash Card #3 and ask the respondent to pick the category that describes the patient best; check only one):*

Never attended school	(0)
Kindergarten, pre kindergarten, or younger	(1)
Grades 1 to 5	(2)
Grades 6-8	(3)
Grades 9-11	(4)
Completed high school	(5)
Some college or post high school education or training	(6)
Bachelor's degree or higher	(7)

17. Is the patient currently employed:

(Yes 1) (No 2)

20. ___

18. What is the patient's current occupation:

_____
specify occupation

19. About how many hours does the patient work each week: ___ ___
hours

20. Which of the following categories best characterizes the patient's occupational history *(show the patient/parent Flash Card #4 and ask the respondent to pick the category that describes the patient best; check only one):*

Never employed	(0)
Laborer	(1)
Clerical	(2)
Professional	(3)
Homemaker	(4)
Other, *(specify):*	(5)

_____
specify

21. Marital status of the patient *(show the patient/parent Flash Card #5 and ask the respondent to pick the category that describes the patient best; check only one):*

Single, never married	(1)
Married or living in marriage-like relationship	(2)
Separated, divorced, or annulled	(3)
Widowed	(4)

22. Combined annual income before taxes of all members of patient's household *(show the patient/parent Flash Card #6 and ask the 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. Previous registration in a NASH CRN study

23. Has the patient ever been assigned an ID number in a NASH CRN study:

(Yes 1) (No 2)

27. ___

24. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

a. Database:	(1)
b. PIVENS:	(1)
c. TONIC:	(1)
d. Other, *(specify):*	(1)

_____
specify

25. ID Number previously assigned to patient *(record patient ID in item 2):*

___ ___ ___ ___

26. Code previously assigned to patient *(record patient code in item 3):*

___ ___ ___

28. ___

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.)

27. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####, zzz

G. Administrative information

28. Clinical Coordinator PIN: ____ ____ ____

29. Clinical Coordinator signature:

_____

30. Date form reviewed:

____ ____–____ ____ ____–____ ____
day 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.

A. Center, patient and visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code *(t0 or code for follow-up visit that is currently open):*

____ ____ ____ ____

6. Form & revision: s d 1

7. Study: NAFLD Database 2 6

B. Surgical pathology report

8. Was a copy of the surgical pathology report for the liver biopsy obtained:

Yes (+ 1) No (* 2)

26. ____

+ 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 year

b. Lobe specimen obtained from *(check only one):*

Right (1)
Left (2)
Unknown (3)

C. Biopsy specimens and stained slides at the clinical center

10. Was a sample of liver tissue obtained for banking:

Yes (*1) No (2)

** If Yes, complete the Liver Tissue Banking (LT) form*

11. Is this visit t0 *(ie, a patient currently in screening*):

Yes (1) No (2)

14.

12. Were you able to obtain stained slides from this biopsy for local evaluation and were they adequate for scoring:

Yes (+1) No (*2)

26.

+ 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:

Yes (1) No (2)

17.

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: ___ ___ (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)

E. Stained slides to be sent to the DCC

17. Is the institution's H & E stained slide to be sent to the DCC:

Yes (1) No (2)

20.

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:

Yes (1) No (2)

20. Is the institution's Masson's trichrome stained slide to be sent to the DCC:

Yes (1) 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:

Yes (1) 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 (1) No (2)

26. ___

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 (1)

26. ___

Other, *(specify):* (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

NAFLD Database 2

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 patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of notification of intent to transfer:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____ ____

6. Form & revision: t n 1

7. Study: NAFLD Database 2 6

B. Last followup visit information

8. Date of last followup visit:

____ ____–____ ____ ____–____ ____
day mon year

9. Visit ID code of last completed followup visit:

____ ____ ____ ____

10. Have cryovial and slide labels been sent to the adopting center:

(Yes 1) (No *2)

* Send the cryovial and slide labels to the adopting center.

C. Current center administrative information

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

12. Clinical coordinator PIN: ____ ____ ____

13. Clinical coordinator signature:

_____

D. Adopting center, patient and visit identification

14. Adopting center ID: ____ ____ ____ ____

15. Patient ID *(must be same as in Section A):*

____ ____ ____ ____

16. Patient code *(must be same as in Section A):*

____ ____ ____

17. Expected date of first followup visit at adopting center:

____ ____–____ ____ ____–____ ____
day mon year

18. Visit ID code for expected first followup visit at adopting center:

____ ____ ____ ____

Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.

E. Adopting center administrative information

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

20. Clinical coordinator PIN: ____ ____ ____

21. Clinical coordinator signature:

_____

Fax form to the DCC. The DCC will key the TN form.

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
IE	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. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: **s** _____ _____

6. Form & revision: **a** **d** **1**

7. Study: FLINT 7

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient (1)
Interview with translator (2)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. 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 1-10 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
(0)	(1)	(2)	(3)	(4)

→ **21.**

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?

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

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
(0)	(1)	(2)	(3)	(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
(0)	(1)	(2)	(3)	(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
(0)	(1)	(2)	(3)	(4)

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

No	Yes, but not in the last year	Yes, during the last year
(0)	(1)	(2)

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
(0)	(1)	(2)

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 Elig 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.

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: s ____ ____

6. Form & revision: b g 2

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):*

Yes (*1) No (2)
11.

**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):*

____ ____–____ ____ ____–____ ____
day mon year
12.

11. Will the patient have a biopsy during screening:

Yes (*1) No (2) Elig

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:

Yes (1) No (2)
20.

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:

Yes (1) No (2)
16.

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

____ ____
age in years

16. Is the patient female and of childbearing potential:

(Yes 1) (No 2) → 20.

17. Is the patient currently pregnant:

(Yes 1) → Elig (No 2)

18. Is the patient currently breast feeding:

(Yes * 1) → C (No 2)

**Caution: Patient cannot be breastfeeding at time of randomization.*

19. Is the patient willing to use effective birth control methods during FLINT:

(Yes 1) (No 2) → Elig

D. Medical history *(C means Caution; condition is exclusionary if study physician agrees with diagnosis; Elig 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: (1)

b. Diabetes type 2: (1)

c. Chronic hepatitis B: (1) → Elig

d. Hepatitis C: (1) → Elig

e. Active autoimmune hepatitis: (1) → C

f. Autoimmune cholestatic liver disorder (PBC): (1) → C

g. Wilson's disease: (1) → C

h. Alpha-1-antitrypsin (A1AT) deficiency: (1) → C

i. Glycogen storage disease: (1)

j. Iron overload: (1) → C

k. Hemochromatosis: (1) → Elig

l. Polycystic liver disease: (1) → C

m. Biliary diversion: (1) → Elig

n. Primary sclerosing cholangitis: (1) → Elig

o. Drug induced liver disease: (1) → Elig

p. Bile duct obstruction: (1) → Elig

q. Gilbert's syndrome: (1)

r. Esophageal or gastric varices on endoscopy: (1) → Elig

s. Bleeding from varices: (1) → Elig

t. Other gastrointestinal bleeding: (1) → C

u. Ascites: (1) → Elig

v. Edema: (1)

w. Hepatic encephalopathy: (1) → Elig

x. Portal hypertension: (1) → Elig

y. Hepatorenal syndrome: (1) Elig

z. Hepatopulmonary syndrome: (1) Elig

aa. Short bowel syndrome: (1) C

ab. Hemophilia *(bleeding disorder):* (1) C

ac. HIV positive: (1) Elig

ad. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

ae. Endocrine disease *(hormonal abnormality):* (1)

af. Hepatocellular carcinoma: (1) Elig

ag. Other malignancy *(cancer):* (1)

ah. Peripheral neuropathy: (1)

ai. Seizure disorder or epilepsy: (1)

aj. Drug allergies: (1)

ak. Hypothyroidism: (1)

al. Hypertension: (1)

am. Cerebrovascular disease: (1)

an. Chronic cholestasis: (1)

ao. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

ap. Pancreatitis: (1)

aq. Cholelithiasis: (1)

ar. Coronary artery disease: (1)

as. Congestive heart failure: (1)

at. Elevated uric acid such as gout: (1)

au. Kidney disease: (1)

av. Polycystic ovary syndrome: (1)

aw. Sleep apnea *(not breathing during sleep):* (1)

ax. Dermatologic disorders: (1)

ay. Myopathy: (1)

az. Myositis: (1)

ba. Major depression: (1)

bb. Schizophrenia: (1)

bc. Bipolar disorder: (1)

bd. Obsessive compulsive disorder: (1)

be. Severe anxiety or personality disorder: (1)

bf. Substance abuse: (1) C

bg. Other *(specify):* (1)

_____
specify

bh. None of the above: (1)

21. Has the patient ever had surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1) Elig

b. Jejunoileal *(or other intestinal)* bypass prior to the diagnosis of NAFLD: (1) Elig

c. Biliopancreatic diversion: (1) Elig

d. Other GI or bariatric surgery *(specify):* (1) C

_____
specify

e. None of the above: (1)

22. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) C No (2)

23. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) Elig No (2)

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

Yes (1) 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)
b. Demeclocycline (Declomycin): (1)
c. Divalproex (Depakote): (1)
d. Doxycycline (Monodox): (1)
e. Methotrexate (Rheumatrex): (1)
f. Minocycline (Dynacin, Minocin): (1)
g. Oxytetracycline (Terramycin): (1)
h. Tetracycline (Achromycin): (1)
i. Valproate sodium (Depacon): (1)
j. Valproic acid (Depakene): (1)
k. Other known hepatotoxin #1 *(specify):* (1)

_____

l. Other known hepatotoxin #2 *(specify):* (1)

_____

m. Other known hepatotoxin #3 *(specify):* (1)

_____

n. None of the above: (1)

25. Were any of the items on 24a-m checked:

Yes (* 1) → C No (2)

**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)
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)

27. Were any of the items 26a-k checked:

Yes (* 1) → C No (2)

**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 estrogen receptor modulators in the past year *(check all that apply):*

a. Boldenone undecylenate (Equipoise): (1)

b. Conjugated estrogen (Premarin/Prempro): (1)

c. Diethylstilbestrol and methyltestosterone (Tylosterone): (1)

d. Esterified estrogen (Estratab, Menest): (1)

e. Estradiol (Estrace): (1)

f. Ethinyl estradiol (Estinyl): (1)

g. Fluoxymesterone (Android-F, Halotestin): (1)

h. Levonorgestrel (Norplant): (1)

i. Medroxyprogesterone (Cycrin, Provera): (1)

j. Megestrol (Megace): (1)

k. Methandrostenolone (Dianabol): (1)

l. Methyltestosterone (Android): (1)

m. Nandrolone (Deca-Durabolin, Durabolin, Hybolin Decanoate, Kabolin): (1)

n. Norethindrone (Micronor): (1)

o. Norgestrel (Ovrette): (1)

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): (1)

t. Raloxifene (Evista): (1)

u. Stanzolol (Winstrol): (1)

v. Tamoxifen (Nolvadex): (1)

w. Testosterone (Depo-Testosterone): (1)

x. Other, *(specify):* (1)

_____

y. Other, *(specify):* (1)

_____

z. None of the above: (1)

29. Were any of the items 28a-y checked:

Yes (* 1) No (2)

C

**Caution: Use of anabolic steroids, tamoxifen, or estrogens at doses greater than those used for hormone replacement for more than 2 weeks in the past year is exclusionary.*

F. Use of antiNASH drugs and supplements

30. Has the patient taken any of these antiNASH drugs in the past 6 months:

Yes (1) No (2)

31.

(If yes,check all that apply):

a. Betaine (Cystadone): (1)

b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)

c. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)

d. S-adenylmethionine (SAM-e): (1)

e. Milk thistle: (1)

f. Probiotics *(any form):* (1)

g. Other *(specify):* (1)

_____
specify

31. Has the patient taken a thiazolidinedione in the past 6 months:

Yes (1) No (2)

G. Use of antiobesity drugs

32. Has the patient taken any antiobesity medications in the past 6 months:

Yes (1) No (2)

33.

(If yes,check all that apply):

a. Dexfenfluramine hydrochloride (Redux): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

c. Methamphetamine hydrochloride (Desoxyn, Gradumet): (1)

d. Orlistat (Xenical): (1)

e. Phendimetrazine tartrate (Adipost, Bontril): (1)

f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): (1)

g. Sibutramine hydrochloride monohydrate (Meridia): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

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): (1)

d. Disulfiram (Antabuse): (1)

e. Hydroxyzine pamoate (Vistaril): (1)

f. Naltrexone hydrochloride (Revia): (1)

g. Other, *(specify):* (1)

_____

h. None of the above: (1)

34. Were any of the items 33a-g checked:

Yes (*1) No (2)

C

**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 (1) No (2)

36.

(If yes, check all that apply):

a. Metformin (Glucophage, Glucophage XR): (1)

b. Acarbose (Precose): (1)

c. Acetohexamide (Dymelor): (1)

d. Chlorpropamide (Diabinese): (1)

e. Glimepiride (Amaryl): (1)

f. Glipizide (Glucotrol, Glucotrol XL): (1)

g. Glyburide (Micronase, DiaBeta, Glynase): (1)

h. Insulin: (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)

_____

36. Has the patient taken any cardiovascular/antihypertensive medications in the past 6 months:

(Yes 1) (No 2)

37.

(If yes, check all that apply):

a. Amlodipine besylate (Norvasc): (1)

b. Aspirin - 81 mg: (1)

c. Atenolol (Tenormin): (1)

d. Benazepril (Lotensin): (1)

e. Captopril (Capoten): (1)

f. Clonidine (Catapres): (1)

g. Digoxin (Lanoxin): (1)

h. Diltiazem (Cardizem): (1)

i. Doxazosin (Cardura): (1)

j. Enalapril (Vasotec): (1)

k. Felodipine (Plendil): (1)

l. Furosemide (Lasix): (1)

m. Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)

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): (1)

s. Nifedipine (Adalat, Procardia): (1)

t. Perhexiline maleate: (1)

u. Propranolol (Inderal): (1)

v. Quinapril (Accupril): (1)

w. Terazosin (Hytrin): (1)

x. Timolol maleate (Blocadren): (1)

y. Valsartan (Diovan): (1)

z. Verapamil (Calan): (1)

aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

37. Has the patient taken any antihyperlipidemic medications in the past 6 months:

(Yes 1) (No 2)

38.

(If yes, check all that apply):

a. Atorvastatin (Lipitor): (1)

b. Colestipol hydrochloride (Colestid): (1)

c. Clofibrate (Abitrate, Atromid-S, Claripex, Novofibrate): (1)

d. Gemfibrozil (Gen-Fibro, Lopid): (1)

e. Fenofibrate (Tricor): (1)

f. Fluvastatin sodium (Lescol): (1)

g. Lovastatin (Mevacor): (1)

h. Nicotinic acid (Niaspan): (1)

i. Pravastatin sodium (Pravachol): (1)

j. Rosuvastatin (Crestor): (1)

k. Simvastatin (Zocor): (1)

l. Other, *(specify):* (1)

_____

38. Has the patient taken any vitamins in the past 6 months:

(Yes 1) (No 2)

39.

(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)

_____

39. Has the patient taken any supplements in the past 6 months:

Yes (1) No (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): (1)

i. Cod liver oil: (1)

j. Coenzyme Q: (1)

k. Dichloroacetate: (1)

l. 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. N-acetyl-cysteine: (1)

u. Potassium (any form): (1)

v. Saw palmetto: (1)

w. Selenium: (1)

x. St. John's Wort: (1)

y. Taurine: (1)

z. Zinc picolinate: (1)

aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

40. Has patient taken any of the following medications or other supplements/medications in the past 6 months:

Yes (1) No (2)

41.

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

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. Other, *(specify):* (1)

_____

J. Administrative information

41. Study Physician PIN: ____ ____ ____

42. Study Physician signature:

_____

43. Clinical Coordinator PIN: ____ ____ ____

44. Clinical Coordinator signature:

_____

45. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

FLINT

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 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 **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 C.

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

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: b p 2

7. Study: FLINT 7

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:

Yes (1) No (* 2)

23. ____

**Patient must be fasting.*

a. Was blood collected for the NIDDK Biosample Repository:

Yes (1)

No, *(specify):* (* 2)

23. ____

_____
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:

____ ____ : ____ ____ (1) (2)
hour minute am pm

10. Number of heparin (green-top) tubes: ____

11. Affix matching heparin tube MACO label:

FLINT Form BP,
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:

FLINT Form BP, Serum 1
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

**Needed during screening and f72 only*

FLINT Form BP, Serum 2*
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

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 20 (screening and f72); 10 (follow-up) 2.0 mL pre-labeled cryovials.

15. Date and time of separation into plasma and serum aliquots

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time of plasma separation:

____ ____ : ____ ____ (1) (2)
hour minute am pm

c. Time of serum separation:

____ ____ : ____ ____ (1) (2)
hour minute am pm

16. Number of aliquots for plasma: ____ ____

17. Number of aliquots for serum: ____ ____

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. Date and time cryovials frozen in -70°C or -20°C

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____:____ ____ (1) am (2) pm
hour minute

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: c g 1

7. Study: FLINT 7

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:

Yes (1) No (2)

10.

9. For which study was it collected *(check all that apply):*

a. Database (1)

b. PIVENS (1)

c. TONIC (1)

d. Database 2 (1)

e. Other, *(specify):* (1)

_____
specify

20.

10. Does the patient consent to genetic research on NAFLD or NASH-related cirrhosis that is currently planned by the study investigators:

Yes (1) No (2)

11. Does the patient consent to future genetic research on NAFLD or NASH-related cirrhosis by this study or other study investigators:

Yes (1) 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:

Yes (1) 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 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):*

Yes (1) No (2)

20. ___

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 (1)

16. ___

No, *(specify):* (2)

_____
specify

20. ___

16. Date and time of blood draw

a. Date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour 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. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: f 9 6

6. Form & revision: c o 1

7. Study: FLINT 7

B. Database participation

8. Does the patient wish to re-enter or join the NAFLD Adult Database 2:

Yes (1) No (2)

11.

9. Has the patient signed the latest version of the NAFLD Adult Database 2 informed consent:

Yes (1) No (*2)

STOP

** Patient must sign the informed consent*

10. Was the patient enrolled in the NAFLD Adult Database 2 previously:

Yes (*1) No (+2)

** 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

c r 2 6. Form and revision

__ 7. Study: **6**=Database 2; **7**=FLINT

__ __ / __ __ __ / __ __ 8. Date of biopsy

B. Slide sequence number

9. 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 (*Specify*):

D. Histology

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

_____ . . . b. Microgranulomas seen: **0**=No; **1**=Yes

_____ . . . c. Large lipogranulomas seen: **0**=No; **1**=Yes

_____ . . . d. Amount of portal, chronic inflammation: **0**=None; **1**=Mild; **2**=More than mild

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

_____ . . . e. Pigmented macrophages (*Kupffer cells*): **0**=Rare/absent; **1**=Many

_____ . . . f. Megamitochondria: **0**=Rare/absent; **1**=Many

_____ 16. Mallory-Denk bodies: **0**=Rare/absent; **1**=Many

_____ 17. Glycogen nuclei: **0**=Rare/absent; **1**=Present in patches

_____ 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 (*does not require trichrome*); **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

_____ 22. Is cirrhosis present? **0**=No ➜ **GOTO item 25**; **1**=Yes

_____ 23. Is this cryptogenic cirrhosis: **0**=No ➜ **GOTO item 25**; **1**=Yes

24. Features suggestive of steatohepatitis etiology for cryptogenic cirrhosis:

_____ . . . a. Mallory-Denk bodies (*rule out cholate stasis*): **0**=Absent; **1**=Present

_____ . . . b. Perisinusoidal fibrosis away from septa: **0**=Absent; **1**=Present

_____ . . . c. Hepatocyte ballooning: **0**=Absent; **1**=Present

_____ . . . d. Megamitochondria: **0**=Absent; **1**=Present

_____ . . . e. Other notable findings: **0**=Absent; **1**=Present; Specify: _____

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 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:

Yes (1) No (2)
14.

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:

Yes (1) No (*2)
15.

**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):*

____ ____ years

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:

Yes (1) No (2)

15. Gender

Male (1)
Female (2)

16. Age: ____ ____ years

If lipid panel was not obtained, skip to item 27.

17. Total cholesterol *(from LR form):*

____ ____ ____
mg/dL

If the patient has total cholesterol greater than 300 mg/dL, an IE form should be completed.

18. HDL cholesterol *(from LR form):*

____ ____ ____
mg/dL

19. LDL cholesterol *(from LR form)*:*

____ ____ ____
mg/dL

**Enter ''GT'' if LDL cannot be calculated due to high triglycerides.*

20. Systolic blood pressure *(from PE form):*

____ ____ ____
mmHg

21. Diastolic blood pressure *(from PE form):*

____ ____ ____
mmHg

22. Are you currently being treated for high blood pressure with medicine prescribed by your doctor:

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

23. Has anyone in your immediate family *(blood-related parent, brother, sister, or child)* been diagnosed with early heart disease *(before age 55 years for male relatives and before 65 years for female relatives):*

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

24. Framingham point scores *(use the ATP III At-a-Glance Quick Desk Reference [NIH Publication No. 01-3305] on page 5 to record gender-specific scores based on the patients risk factors. Circle ''+'' or ''-'' as appropriate. Key ''+#'' or ''-#''; if 0 for an item with +/-, key ''+0'' or ''+00''.)*

a. Age score *(based on item 16):* +/- ____ ____ points

b. Total cholesterol score *(based on items 16 and 17):* ____ ____ points

c. Smoking score *(based on items 9 or 14, and 16):* ____ points

d. HDL score *(based on item 18):* +/- ____ points

e. Systolic blood pressure score *(based on items 20 and 22):* ____ points

25. Point total *(Add items 24a-e):* +/- ____ ____ points

26. 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 5, use the point total [item 25] to convert into gender-specific 10 year risk):*

____ ____ %

If 10 year risk < 1, record ''00''. If 10 year risk ≥ 30, record ''30''.

D. ATP III guidelines

27. Have you been diagnosed with type 1 or type 2 diabetes:

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

28. Have you been diagnosed with clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

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

29. ⌐

(If yes, check all that apply)

a. Clinical CHD: ( ) (1)

b. Symptomatic carotid artery disease: ( ) (1)

c. Peripheral arterial disease: ( ) (1)

d. Abdominal aortic aneurysm: ( ) (1)

29. Was ''Yes'' checked for either item 27 or 28 or was LDL unknown (''GT'' in item 19 or lipid panel not obtained):

(Yes 1) (No 2)

31.

30. Is 10-year Framingham heart attack risk estimate 22% (item 26) or more:

(Yes 1) (No 2)

33.

31. Is LDL cholesterol (item 19) less than 100 mg/dL or was LDL unknown (''GT'' in item 19 or lipid panel not obtained):

(Yes 1) (No 2)

40.

32. Is LDL cholesterol (item 19) 130 mg/dL or more:

(Yes * 1) (No † 2)

40. **40.**

**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):* (1)

b. SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or on antihypertensive medication *(based on items 20, 21, and 22):* (1)

c. HDL cholesterol less than 40 mg/dL *(based on item 18):* (1)

d. Family history of premature CHD *(see item 23):* (1)

e. Age in men ≥ 45 years or age in women ≥ 55 years *(based on items 15 and 16):* (1)

f. HDL cholesterol 60 mg/dL or more *(based on item 18):* (1)

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):

(Yes 1) (No 2)

38.

36. Is LDL cholesterol less than 130 mg/dL:

(Yes 1) (No 2)

40.

37. Is 10-year Framingham heart attack risk estimate between 10 and 20%, inclusive or LDL cholesterol 160 mg/dL or more:

Yes (*1) → **40.**
No (†2) → **40.**

**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:

Yes (*1) → **40.**
No (2)

**Refer for cholesterol management with LDL-lowering drug therapy (see FLINT SOP V).*

39. Is LDL cholesterol between 160 and 189 mg/dL, inclusive:

Yes (†1)
No (2)

†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)
b. Angina: (1)
c. Stroke: (1)
d. Cerebrovascular disease: (1)
e. Coronary artery disease: (1)
f. Congestive heart failure: (1)
g. Peripheral vascular disease: (1)
h. Other cardiovascular disease *(specify):* (1)

_____
specify

i. None of the above: (1)

F. Administrative information

41. Study Physician PIN: ____ ____ ____

42. Study Physician signature:

_____

43. Clinical Coordinator PIN: ____ ____ ____

44. Clinical Coordinator signature:

_____

45. Date form reviewed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

Men

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 Cholesterol	Points				
	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
3	1
4	1
5	2
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 _____%

Women

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 Cholesterol	Points				
	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

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____

6. Form & revision: d r 1

7. Study: FLINT 7

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Health care provider or NASH CRN staff: (1)
d. Newspaper: (1)
e. Funeral parlor/home: (1)
f. Medical record: (1)
g. Medical examiner: (1)
h. Coroner: (1)
i. Other *(specify):* (1)

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

11. Cause of death
(Study Physician: use whatever knowledge you have and your best medical judgment to best characterize the cause of death; check only one):

Heart disease (1)
Stroke (2)
Liver disease (3)
Malignancy (4)
Other *(specify):* (5)

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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 Elig is checked for any item, the patient is not eligible for FLINT and the form should not be keyed. If c 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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: h f 2

7. Study: FLINT 7

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)
b. Masson's trichrome: (1)
c. Iron: (1)

10. Biopsy length: ____ ____ mm

C. NASH evaluation (use H & E and Masson's trichrome slides only)

11. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5% (0) Elig
5-33% (1)
34-66% (2)
> 66% (3)

b. Location:

Zone 3 (0)
Zone 1 (1)
Azonal (2)
Panacinar (3)

12. Fibrosis stage *(Masson's trichrome stain)*

0: None (0)
1a: Zone 3, perisinusoidal (requires trichome) (1)
1b: Zone 3, perisinusoidal (easily seen on H & E) (2)
1c: Portal/periportal only (3)
2: Zone 3 and periportal, any combination (4)
3: Bridging (5)
4: Cirrhosis (6) Elig

13. Inflammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

0 (0) Elig

< 2 / 20x mag (1)

2-4 / 20x mag (2)

> 4 / 20x mag (3)

b. Amount of portal, chronic inflammation:

None to minimal (0)

Mild (1)

More than mild (2)

14. Hepatocellular ballooning:

None (0) Elig

Few (1)

Many (2)

15. Is steatohepatitis present:

No (1) Elig

Suspicious/borderline/indeterminate (2)

Yes, definite (3)

D. Exclusion of other liver disease

16. Is there evidence of primary biliary cirrhosis:

Yes (* 1) C No (2)

** Caution: Primary biliary cirrhosis is exclusionary*

17. Is there evidence of Wilson's disease:

Yes (* 1) C No (2)

** Caution: Wilson's disease is exclusionary*

18. Features of chronic cholestatic liver disease *(check all that apply)*

a. Bile duct loss/infiltration/sclerosis: (* 1) C

b. Florid duct lesions: (1)

c. Cholate stasis: (1)

d. Copper deposition: (1)

e. Other *(specify):* (1)

_____

f. None: (1)

** 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: (1)

b. Inflammation suggestive of AIH, HCV: (* 1) C

c. Pigment suggestive of HH: (* 1) C

d. Globules suggestive of A1AT: (* 1) C

e. Hepatocellular changes suggestive of HBV: (* 1) C

f. Granulomas suggestive of sarcoid, PBC, infection: (* 1) C

g. Other *(specify):* (1)

_____

h. None: (1)

** 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: Yes (1) No (2)

Elig

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.

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: f ____ ____

6. Form & revision: h i 2

7. Study: FLINT 7

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:

(Yes *1) (No 2)

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

D. Alcohol consumption (AUDIT-C) since the last visit

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

- Never (0)

14. ____

- Monthly or less (1)
- 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 (4)

13. 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. Recent medical history

14. Has the patient been diagnosed with any of the following since the last visit *(check all that apply; source of information can be interview and/or chart review)*

a. Diabetes type 1: (1)
b. Diabetes type 2: (1)
c. Chronic hepatitis B: (1)
d. Hepatitis C: (1)
e. Active autoimmune hepatitis: (1)
f. Autoimmune cholestatic liver disorder (PBC): (1)
g. Wilson's disease: (1)
h. Alpha-1-antitrypsin (A1AT) deficiency: (1)
i. Glycogen storage disease: (1)
j. Iron overload: (1)
k. Hemochromatosis: (1)
l. Polycystic liver disease: (1)
m. Biliary diversion: (1)
n. Primary sclerosing cholangitis: (1)
o. Drug induced liver disease: (1)
p. Bile duct obstruction: (1)
q. Gilbert's syndrome: (1)
r. Esophageal or gastric varices on endoscopy: (1)
s. Bleeding from varices: (1)
t. Other gastrointestinal bleeding: (1)
u. Ascites: (1)
v. Edema: (1)
w. Hepatic encephalopathy: (1)
x. Portal hypertension: (1)
y. Hepatorenal syndrome: (1)
z. Hepatopulmonary syndrome: (1)
aa. Short bowel syndrome: (1)
ab. Hemophilia *(bleeding disorder):* (1)
ac. HIV positive: (1)
ad. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)
ae. Endocrine disease *(hormonal abnormality):* (1)
af. Hepatocellular carcinoma: (1)
ag. Other malignancy *(cancer):* (1)
ah. Peripheral neuropathy: (1)
ai. Seizure disorder or epilepsy: (1)
aj. Drug allergies: (1)
ak. Hypothyroidism: (1)
al. Hypertension: (1)
am. Cerebrovascular disease: (1)
an. Chronic cholestasis: (1)
ao. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)
ap. Pancreatitis: (1)
aq. Cholelithiasis: (1)
ar. Coronary artery disease: (1)
as. Congestive heart failure: (1)
at. Elevated uric acid such as gout: (1)
au. Kidney disease: (1)
av. Polycystic ovary syndrome: (1)
aw. Sleep apnea *(not breathing during sleep):* (1)
ax. Dermatologic disorders: (1)
ay. Myopathy: (1)
az. Myositis: (1)
ba. Major depression: (1)
bb. Schizophrenia: (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 surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1)
b. Jejunoileal *(or other intestinal)* bypass: (1)
c. Biliopancreatic diversion: (1)
d. Other GI or bariatric surgery *(specify):* (1)

_____

e. None: (1)

16. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) No (2)

17. Since the last visit, has the patient received:

a. Liver transplant: Yes (1) No (2)

b. Any other organ, limb, or bone marrow transplant: Yes (1) No (2)

18. Since the last visit, has the patient had ER visits or hospitalizations:

Yes (* 1) No (2)

19. ⌊

** Complete an Interim Event Report (IE) form*
If Yes, specify reason and list dates:

_____

_____

If none for items 18a or 18b, enter "00".

a. Number of hospitalizations: ____ ____ # of hospitalizations

b. Number of Emergency Room visits: ____ ____ # of visits

19. Since the last visit, has the patient had any serious health problem or adverse events not already reported:

Yes (* 1) No (2)

20. ⌊

** Complete an Interim Event Report (IE) form*
If Yes, specify and list dates:

_____

_____

F. Drugs historically associated with NAFLD

20. Has the patient used any of the following since last visit:

Yes (1) No (2)

21. ⌊

(If yes, check all that apply):

a. Amiodarone (Cordarone, Pacerone): (1)
b. Demeclocycline (Declomycin): (1)
c. Divalproex (Depakote): (1)
d. Doxycycline (Monodox): (1)
e. Methotrexate (Rheumatrex): (1)
f. Minocycline (Dynacin, Minocin): (1)
g. Oxytetracycline (Terramycin): (1)
h. Tetracycline (Achromycin): (1)
i. Valproate sodium (Depacon): (1)
j. Valproic acid (Depakene): (1)
k. Other known hepatotoxin #1 *(specify):* (1)

_____

l. Other known hepatotoxin #2 *(specify):* (1)

_____

m. Other known hepatotoxin #3 *(specify):* (1)

_____

21. Has the patient taken any systemic glucocorticoids since last visit:

Yes (1) No (2)

22. ⌊

(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): (1)
j. Other, *(specify):* (1)

_____

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) No (2)

23.

(If yes, check all that apply):

a. Boldenone undecylenate (Equipoise): (1)
b. Conjugated estrogen (Premarin/Prempro): (1)
c. Diethylstilbestrol and methyltestosterone (Tylosterone): (1)
d. Esterified estrogen (Estratab, Menest): (1)
e. Estradiol (Estrace): (1)
f. Ethinyl estradiol (Estinyl): (1)
g. Fluoxymesterone (Android-F, Halotestin): (1)
h. Levonorgestrel (Norplant): (1)
i. Medroxyprogesterone (Cycrin, Provera): (1)
j. Megestrol (Megace): (1)
k. Methandrostenolone (Dianabol): (1)
l. Methyltestosterone (Android): (1)
m. Nandrolone (Deca-Durabolin, Durabolin, Hybolin Decanoate, Kabolin): (1)
n. Norethindrone (Micronor): (1)
o. Norgestrel (Ovrette): (1)
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): (1)
t. Raloxifene (Evista): (1)
u. Stanzolol (Winstrol): (1)
v. Tamoxifen (Nolvadex): (1)
w. Testosterone (Depo-Testosterone): (1)
x. Other, *(specify):* (1)

_____

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.

(If yes, check all that apply):

a. Betaine (Cystadone): (1)
b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
c. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
d. S-adenylmethionine (SAM-e): (1)
e. Milk thistle: (1)
f. Probiotics *(any form):* (1)
g. Other *(specify):* (1)

_____
specify

24. Has the patient taken a thiazolidinedione since last visit:

Yes (1) No (2)

H. Use of antiobesity drugs

25. Has the patient taken any antiobesity medications since last visit:

Yes (1) No (2)

26.

(If yes, check all that apply):

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

_____

i. Other, *(specify):* (1)

_____

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 (1) No (2)

27.

(If 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) No (2)

28.

(If yes, check all that apply):

a. Metformin (Glucophage, Glucophage XR): (1)
b. Gemfibrozil (Gen-Fibro, Lopid): **VOID**
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)
j. Miglitol (Glycet): (1)
k. Nateglinide (Starlix): (1)
l. Pioglitazone (Actos): (1)
m. Repaglinide (Prandin): (1)
n. Rosiglitazone (Avandia): (1)
o. Tolazamide (Tolinase): (1)
p. Tolbutamide (Orinase): (1)
q. Other, *(specify):* (1)

_____

28. Has the patient taken any cardiovascular/antihypertensive medications since last visit:

Yes (1) No (2)

29.

(If yes, check all that apply):

a. Amlodipine besylate (Norvasc): (1)
b. Aspirin - 81 mg: (1)
c. Atenolol (Tenormin): (1)
d. Benazepril (Lotensin): (1)
e. Captopril (Capoten): (1)
f. Clonidine (Catapres): (1)
g. Digoxin (Lanoxin): (1)
h. Diltiazem (Cardizem): (1)
i. Doxazosin (Cardura): (1)
j. Enalapril (Vasotec): (1)
k. Felodipine (Plendil): (1)
l. Furosemide (Lasix): (1)
m. Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)
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): (1)
s. Nifedipine (Adalat, Procardia): (1)
t. Perhexiline maleate: (1)
u. Propranolol (Inderal): (1)
v. Quinapril (Accupril): (1)
w. Terazosin (Hytrin): (1)
x. Timolol maleate (Blocadren): (1)
y. Valsartan (Diovan): (1)
z. Verapamil (Calan): (1)
aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

29. Has the patient taken any antihyperlipidemic medications since last visit:

Yes (1) No (2)

30.

(If yes, check all that apply):

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

_____

30. Has the patient taken any vitamins since last visit:

Yes (1) 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 (1) No (2)

32.

(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): (1)
i. Cod liver oil: (1)
j. Coenzyme Q: (1)
k. Dichloroacetate: (1)
l. 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. N-acetyl-cysteine: (1)
u. Potassium (any form): (1)
v. Saw palmetto: (1)
w. Selenium: (1)
x. St. John's Wort: (1)
y. Taurine: (1)
z. Zinc picolinate: (1)
aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

32. Has patient taken any of the following medications or other supplements/medications since last visit:

Yes (1) No (2)

33.

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

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. Other, *(specify):* (1)

_____

K. Administrative information

33. Study Physician PIN: ____ ____ ____

34. Study Physician signature:

_____

35. Clinical Coordinator PIN: ____ ____ ____

36. Clinical Coordinator signature:

_____

37. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

FLINT

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____
if report not associated with a visit, fill in ''n''

6. Form & revision: i e 3

7. Study: FLINT 7

B. Visit interval identification

8. Most recently completed visit (screening or followup)

a. Date: ____ ____–____ ____ ____–____ ____
day mon year

b. Visit code: ____ ____ ____

C. Patient information

9. Gender:

Male (1)
Female (2)

10. Age at time of event: ____ ____
years

D. Event description

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

First report (1)
Followup report (2)

12. Date event started:

____ ____–____ ____ ____–____ ____
day mon year

13. Nature of event *(check all that apply)*

a. Drug dispensing mixup: (1)
b. Medication related event: (1)
c. Study procedure related event: (1)
d. Severe allergic reaction: (1)
e. Drug interactions: (1)
f. Worsening of a co-morbid illness: (1)
g. Patient reported symptom of hepatotoxicity: (1)
h. Hypoglycemia/hyperglycemia: (1)
i. Diabetes: (1)
j. Pregnancy *(patient):* (*1)
k. Other *(specify):* (1)

_____

_____

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

14. Describe event:

_____

_____

_____

_____

_____

_____

For items 15, 16, and 17, please refer to CTCAE v3.0 available at www.nashcrn.com; click on Studies and then FLINT.

15. Identify body system *(check all that apply)*

a. Auditory/ear: (1)
b. Allergy/immunologic: (1)
c. Ocular/visual: (1)
d. Hepatobiliary/pancreatic: (1)
e. Infection: (1)
f. Constitutional symptoms: (1)
g. Psychiatric: (1)
h. Cardiovascular: (1)
i. Dermatologic/skin: (1)
j. Endocrine/metabolic: (1)
k. Gastrointestinal/digestive: (1)
l. Lymphatic/blood: (1)
m. Musculoskeletal: (1)
n. Neurologic: (1)
o. Pulmonary/respiratory: (1)
p. Renal/genitourinary: (1)
q. Sexual/reproductive: (1)
r. Other *(specify):* (1)

_____
specify other body system

s. None of the above: (1)

16. Short name for event if applicable:

Not applicable (0)

_____

_____

17. 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	(4)
Grade 5 - Death	(*5)

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

18. Randomization in FLINT

a. Has patient been randomized in FLINT:

Yes (1) No (2)

26.

b. Date randomized in FLINT:

____ ____–____ ____ ____–____ ____

day mon year

19. Is the patient currently receiving the FLINT study drug:

Yes (1) No (2)

20. Patient's history of treatment with FLINT study drug

a. How long has patient been on study drug:

_____

b. Have there been any treatment interruptions or restarts:

Yes (1) No (2)

Include stop/restart dates and reasons:

_____

_____

_____

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

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

22. Is this a serious adverse event:

Yes (1) No (2)

23.

If Yes, then select all the reasons that apply:

a. Severity Grade 4 or 5: (1)

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: (1)

e. Congenital abnormality or birth defect: (1)

23. Is this an unexpected adverse event:

Yes (1) No (2)

25.

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	(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:

Yes (*1) 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	(3)

28.

28.

27. Date adverse event resolved:

____ ____–____ ____ ____–____ ____
day mon year

28. What action was taken:

29. Other comments on event:

E. Administrative information

30. Clinical Coordinator PIN: ____ ____ ____

31. Clinical Coordinator signature:

32. Study Physician PIN: ____ ____ ____

33. Study Physician signature:

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.

FLINT

LD – Lifetime Drinking History (Skinner)

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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: **S** _____ _____

6. Form & revision: **l** **d** **1**

7. Study: FLINT 7

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):

Yes (1) No (2)

81. ◄

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)*	(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)*:

		Positive	Negative	Neutral
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)

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 ____ ____ ____ %

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 ____ ____ ____ %

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":

Yes (1) No (2)

81. ↵

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:

Yes (1) No (2)

30. ↵

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)*:

	Positive	Negative	Neutral
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)

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 ____ ____ ____ %

With others ____ ____ ____ %

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 be "000")*:

Morning ____ ____ ____ %

Afternoon ____ ____ ____ %

Evening ____ ____ ____ %

E. Next 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 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 (1) No (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:

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")*:

Beer ____ ____ ____ %

Liquor ____ ____ ____ %

Wine ____ ____ ____ %

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)

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

Yes (1) No (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)*:

	Positive	Negative	Neutral
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":

Yes (1) No (2)

81. ◄

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

a. Years: ____ ____ yrs

b. Months: ____ ____ mos

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:

____ ____ # drinks

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

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 (1) No (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)*:

	Positive	Negative	Neutral
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"*:

Yes (1) No (2)

81. ◀

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

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

____ ____
drinks

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

____ ____
days

61. 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.*)

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 ____ ____ ____
%

Liquor ____ ____ ____
%

Wine ____ ____ ____
%

63. 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)

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

Yes	No
(1)	(2)

→ **66.**

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 effect)*:

		Positive	Negative	Neutral
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)

66. 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 ____ ____ ____
%

67. 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 ____ ____ ____
%

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 (1) No (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.*)

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 ____ ____ ____ %

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)

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

Yes (1) No (2)

78. ◄

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)*:

	Positive	Negative	Neutral
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)

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 all 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 _____ _____ _____ %

Evening _____ _____ _____ %

I. Number of phases

80. Are there any additional subsequent phases:

Yes (* 1) No (2)

***** *If yes, complete a second LD form.*
Skip sections B and C on second form.

J. Administrative information

81. Clinical Coordinator PIN: _____ _____ _____

82. Clinical Coordinator signature:

_____

83. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
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 (LMg) is checked for any item, then the form should not be keyed.

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: 1 r 1

7. Study: FLINT 7

B. Hematology

Required at visits s, f24, f48, f72, and f96.

8. Is hematology testing required at this visit:

Yes (1) No (2)

15.

9. Date of blood draw for complete blood 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 FLINT visit time window guide).

10. Hemoglobin: ____ ____ • ____ ____ g/dL

11. Hematocrit: ____ ____ • ____ ____ %

12. Mean corpuscular volume (MCV):

____ ____ ____ fL

13. White blood cell count (WBC):

____ ____ • ____ ____ 10^3 cells/ µL or 10^9 cells/L

14. Platelet count:

____ ____ ____, ____ ____ ____ cells/mm^3

If platelets < 100,000 cells/mm^3 (mm^3 = µL) at screening, patient is ineligible.

C. Chemistries

Required at visits s, f24, f48, f72, and f96.

15. Is metabolic panel required at this visit:

Yes (1) No (2)

28.

16. 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 FLINT visit time window guide).

17. Sodium: ____ ____ ____ mEq/L

18. Potassium: ____ ____ • ____ ____ mEq/L

19. Chloride: ____ ____ ____ mEq/L

20. Bicarbonate: ____ ____ • ____ ____ mEq/L

21. Calcium: ____ ____ • ____ ____ mg/dL

22. Phosphate: ____ ____ • ____ mg/dL

23. Blood urea nitrogen (BUN): ____ ____ mg/dL

24. Creatinine *(if serum creatinine ≥ 2.0 mg/dL, patient is ineligible):*

____ ____ • ____ mg/dL

25. Uric acid: ____ ____ • ____ mg/dL

26. Albumin *(if albumin < 3.2 g/dL, patient is ineligible):*

____ • ____ g/dL

27. Total protein: ____ ____ • ____ g/dL

D. Prothrombin time and INR

Required at visits s and f72.

28. Are the prothrombin time and INR required at this visit:

Yes (1) No (2)

32.

29. Date of blood draw for prothrombin time and INR:

____ ____–____ ____ ____–____ ____
day mon year

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 FLINT visit time window guide).

30. Prothrombin time (PT): ____ ____ • ____ sec

31. International normalized ratio (INR) *(if INR > 1.3, patient is ineligible):*

____ • ____

E. Hemoglobin A1c

Required at visits s, f24, f48, f72, and f96.

32. Is HbA1c required at this visit:

Yes (1) No (2)

35.

33. Date of blood draw for HbA1c:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within the required time window; within 60 days of randomization or in the time window for the follow-up visit (check the patient's FLINT visit time window guide).

34. HbA1c *(if HbA1c is ≥ 9.5% within 60 days of randomization, patient is ineligible):*

____ ____ • ____ %

F. Liver panel

Required at all visits.

35. 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 FLINT visit time window guide).

36. Bilirubin (total): ____ ____ • ____ mg/dL

37. Bilirubin (conjugated or direct) *(if direct bilirubin > 1.3 mg/dL, patient is ineligible):*

____ ____ • ____ mg/dL

38. Aspartate aminotransferase (AST)

____ ____ ____ U/L

a. Upper limit of normal: ____ ____ ____ U/L

39. Alanine aminotransferase (ALT)
(if ALT > 300 U/L at screening, patient is ineligible)

____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

40. Alkaline phosphatase ____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
U/L

41. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

G. Fasting lipid profile

Required at all visits

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw.

42. Was participant fasting for at least 8 hours prior to blood draw:

Yes (1) No* (2)

**12 hour fasting is preferred, but will accept non-fasting lipid values.*

43. 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 FLINT visit time window guide).

a. Triglycerides: ____ ____ ____ ____
mg/dL

b. Total cholesterol: ____ ____ ____
mg/dL

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/oral glucose tolerance test

Fasting glucose and insulin are required at all visits; the 2 hour OGTT is required at visits s and f72 for nondiabetics.

The 2 hour oral glucose tolerance test will be performed in the morning after a 12-hour overnight fasting. Blood samples will be obtained for measurements of serum glucose and insulin at baseline and 2 hours (120 minutes) after oral administration of a flavored glucose solution in a dose of 2 g/kg (75 g maximum).

44. Was participant fasting for at least 8 hours:

Yes (1) No* (2)
49.

**Patient must be fasting; 12 hour fasting is preferred. Fasting glucose and insulin must be obtained at visit s.*

45. Date of blood draw for fasting glucose and insulin/OGTT:

____ ____–____ ____ ____–____ ____
day mon year

Date must be within 90 days of liver biopsy or in the time window for the followup visit (check the patient's FLINT visit time window guide).

46. Result of baseline fasting glucose/insulin levels

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____
µU/mL

47. Is glucose tolerance test (OGTT) required at this visit *(the 2 hour OGTT is required at visits s and f72 for nondiabetics):*

Yes (1)
No (2)
49.
No, patient is diabetic (3)
49.

48. OGTT results at 2 hours

a. Serum glucose: ____ ____ ____
mg/dL

b. Serum insulin: ____ ____ ____ • ____
µU/mL

I. Pregnancy test

Required at all study visits, if applicable.

49. Is pregnancy test applicable:

Yes (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:

Yes (1) No (2)

→ **54.**

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:

Yes (1) No (2)

→ Elig

K. Administrative information

54. Study Physician PIN: ____ ____ ____

55. Study Physician signature:

_____

56. Clinical Coordinator PIN: ____ ____ ____

57. Clinical Coordinator signature:

_____

58. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

FLINT

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 Elig 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: 1 s 1

7. Study: FLINT 7

B. Screening etiologic tests

8. Date of blood draw for serological assays to exclude viral causes of chronic liver disease:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 1 year prior to screening.

If the patient is judged by Study Physician to have a high-risk lifestyle, repeat if date is greater than 3 months prior to screening.

a. Hepatitis B surface antigen (HBsAg):
Positive (1) Elig
Negative (2)

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 (1)
Negative (2)
Not available (3)

d. Hepatitis C virus RNA (HCV RNA):
Positive (1) Elig
Negative (2)
Not available (3)

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 (1) → EHg

Negative (2)

C. Iron

9. Date of blood draw for iron overload screening:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 1 year prior to screening.

a. Iron: ____ ____ ____ µg/dL

b. Total iron binding capacity: ____ ____ ____ µg/dL

c. Ferritin: ____ ____ ____ ____ ng/mL

10. Is hepatic iron index available:

Yes (1) No (2) → 12.

11. Hepatic iron index: ____ • ____ µMol/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+:

Yes (1) No (2) → 15.

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:

Yes (1) No (2) → 18.

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 ____ ____ • ____ ____ mg/dL

a. Upper limit of normal: ____ ____ • ____ ____ mg/dL

b. Lower limit of normal: ____ ____ • ____ ____ mg/dL

c. Is ceruloplasmin < LLN:

Yes (*1) → C No (2)

**Check liver biopsy histology findings for Wilson's disease.*

F. Alpha-1 antitrypsin

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

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 5 years prior to screening.

19. Alpha-1 antitrypsin (A1AT) ____ ____ ____ mg/dL

a. Upper limit of normal: ____ ____ ____ mg/dL

b. Lower limit of normal: ____ ____ ____ mg/dL

20. A1AT phenotype:

a. Pi Z heterozygote:

Yes (1)
No (2)
Unknown (3)

b. Pi ZZ homozygote:

Yes (1)
No (2)
Unknown (3)

21. A1AT deficiency as a contributor to liver disease *(physician judgment):*

Yes (1) → Elig
No (2)

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):

Positive (*1)
Negative (2)

24.

**If positive ANA value, complete either a or b depending on laboratory results:*

a. Titer *(record only the denominator):*

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____

24. Date of blood draw for antismooth muscle antibody tests:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 5 years prior to screening.

25. Antismooth muscle antibody (ASMA):

Positive (*1)
Negative (2)

26.

**If positive ASMA value, complete either a or b depending on laboratory results:*

a. Titer *(record only the denominator):*

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____

26. Date of blood draw for antimitochondrial antibody tests:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 5 years prior to screening.

27. Antimitochondrial antibody (AMA):

Positive (*1)
Negative (2)

28.

**If positive AMA value, complete either a or b depending on laboratory results:*

a. Titer *(record only the denominator):*

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____

H. Administrative information

28. Study Physician PIN: ____ ____ ____

29. Study Physician signature:

_____

30. Clinical Coordinator PIN: ____ ____ ____

31. Clinical Coordinator signature:

_____

32. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

FLINT

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code *(s or f72):* ____ ____ ____

6. Form & revision: 1 t 2

7. Study: FLINT 7

B. Liver biopsy/RNA*later*® Solution storage procedures

8. Date of biopsy:

____ ____–____ ____ ____–____ ____
day mon year

9. Was the liver tissue obtained from a needle core biopsy *(as opposed to a wedge biopsy):*

Yes (1) No (2)

10. Was liver tissue placed in RNA*later*® Solution preferably within 1 minute, but no more than 5 minutes after biopsy:

Yes (1) No (*2)

13.

* *Discard liver tissue*

11. Was liver tissue refrigerated at 4° C overnight, then transferred to freezer for storage:

Yes (1) No (2)

12.

a. If no, describe conditions of local storage:

_____

_____

C. Cryovial label

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):*

D. Administrative information

13. Clinical Coordinator PIN: ____ ____ ____

14. Clinical Coordinator signature:

_____

15. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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:

Yes (1) No (*2)

17.

B. Consent

9. Has the patient signed the FLINT MRI consent:

Yes (1) No (*2)

17.

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

C. MRI results and information

10. Was an MRI performed:

Yes (1) No (*2)

12.

** Complete item 11, then skip to item 17.*

11. Reason MRI not performed *(check all that apply)*

a. Patient was not fasting: (1)

b. Patient suffers from extreme claustrophobia: (1)

c. Patients weight or girth exceeds MRI scanner capabilities: (1)

d. Other *(specify):* (1)

_____

17.

12. Technician name:

_____
print name

13. Date and time of MRI:

____ ____–____ ____ ____–____ ____
day mon year

a. Time:

____ ____ : ____ ____ (1) am (2) pm
hour minute

FLINT

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. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed: ____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: f ____ ____

6. Form & revision: m v 1

7. Study: FLINT 7

B. Reason for completion of this form

8. Was the entire visit missed:
(Yes 1) (No 2)
11.

C. Missed visit information

9. Reason for missed visit *(check all that apply)*

a. Patient was ill: (1)

b. Patient was temporarily away from area: (1)

c. Patient refused to return: (1)

d. Patient has permanently moved from the area: (1)

e. Unable to contact patient: (1)

f. Other *(specify):* (1)

_____
specify

10. Steps taken to avoid missing the visit *(check all that apply)*

a. Telephoned patient: (1)

b. Mailed reminder card: (1)

c. Other *(specify):* (1)

_____
specify

14.

D. Missed form information

11. Check form(s) not completed *(check all that apply)*

a. Blood Processing for Plasma and Serum (BP): (1)

b. Follow-up Medical History (HI): (1)

c. Laboratory Results - Tests Done During Screening and Followup (LR): (1)

d. Liver Tissue Banking (LT): (1)

e. Physical Examination (PE): (1)

f. Focused Physical Examination (PF): (1)

g. SF-36v2 Health Survey (QF): (1)

h. Study Drug Dispensing and Return (RD): (1)

i. Liver Biopsy Materials Documentation (SD): (1)

j. MRI Consent and Documentation (MR): (1)

k. 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. Administrative 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

FLINT

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: p e 1

7. Study: FLINT 7

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement:

____ ____ ____ • ____

b. Weight, 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
waist circumference

c. Units:

Inches (1)
Centimeters (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
hip circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
hip circumference

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral)*

a. Degrees: ___ ___ ___ • ___

b. Scale:
Fahrenheit (1)
Centigrade (2)

13. Blood pressure

a. Systolic: ___ ___ ___ mmHg

b. Diastolic: ___ ___ ___ mmHg

14. Resting radial pulse: ___ ___ ___ beats/minute

15. Respiratory rate: ___ ___ breaths/minute

C. Examination findings

16. Chest and lungs:
Normal (1)
Abnormal (2)
17. ___

_____
specify abnormality

17. Heart:
Normal (1)
Abnormal (2)
18. ___

_____
specify abnormality

18. Abdomen abnormalities present *(check all that apply):*
a. None: (1)
b. Ascites: (1)
c. Obese: (1)
d. Splenomegaly: (1)
e. Hepatomegaly: (1)

If Yes, span at right midclavicular line:

___ ___ • ___ cm

19. Focused liver signs *(check all that apply)*
a. None: (1)
b. Jaundice: (1)
c. Palmar erythema: (1)
d. Contractures: (1)
e. Pedal edema: (1)
f. Spider angiomata: (1)
g. Asterixis: (1)
h. Hepatic encephalopathy: (1)
i. Wasting: (1)
j. Fetor: (1)
k. Pruritus: (1)
l. Other, *(specify):* (1)

_____
specify

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

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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: f ____ ____

6. Form & revision: p f 1

7. Study: FLINT 7

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:
Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:
Pounds (1)
Kilograms (2)

10. Temperature *(oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:
Fahrenheit: (1)
Centigrade: (2)

11. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

12. Resting radial pulse: ____ ____ ____ beats/minute

13. Respiratory rate: ____ ____ breaths/minute

C. Administrative information

14. Clinical Coordinator ID: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

FLINT

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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____

6. Form & revision: q f 1

7. Study: FLINT 7

B. Administrative information
(To be completed by clinical center staff after survey is completed.)

8. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature: _____

9. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

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:

Circle 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?

Circle 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 label here

Patient ID: __ __ __ __

Patient code: __ __ __

Visit code: __ __ __

12. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Activities	Circle one		
	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 past 4 weeks, how much of the time 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				
	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 amount of time 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 kind 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 past 4 weeks, how much of the time 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				
	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 amount of time 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 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	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

16. How much bodily pain have you had during the past 4 weeks?

Circle one

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

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**	**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 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

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

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.

FLINT

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, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: r c 1

7. Study: FLINT 7

B. FLINT participation

8. Date in item 4 of original FLINT RG form: ____ ____–____ ____ ____–____ ____
day mon year

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature: _____

11. Date form reviewed: ____ ____–____ ____ ____–____ ____
day mon year

FLINT

RD – Study Drug Dispensing and Return

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.

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: r d 1

7. Study: FLINT 7

B. Study drug dispensing

8. Is this a second form for returning additional drug bottles at this visit:

Yes (* 1) → 16.
No (2)

* *Key first form before this form.*

9. Will study drug be dispensed today:

Yes (1) → 11.
No (2)

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: (1)
d. Other *(specify)*: (1)

_____
specify

→ 16.

11. How many bottles were dispensed: ____ (1-3)

Bottle tear-off label

12.

Affix label here

13.

Affix label here

14.

Affix label here

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:

Yes	No
(1)	(2)

23.

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:

Yes	No
(* 1)	(2)

**If yes, complete a second RD form using visit code "n."*

E. Administrative information

23. Study Physician PIN: _____ _____ _____

24. Study Physician signature:

_____

25. Clinical Coordinator PIN: _____ _____ _____

26. Clinical Coordinator signature:

_____

27. Date form reviewed:

_____ _____ - _____ _____ _____ - _____ _____
day mon year

FLINT

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 STOP condition is checked in section B or C.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: r g 1

7. Study: FLINT 7

B. Consent

8. Has the patient signed the FLINT informed consent statement:

Yes (1) No (2) STOP

C. Information about patient

9. Patient age

a. Date of birth:

____ ____–____ ____ ____–____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

b. Age at last birthday: ____ ____
years

c. Is patient at least 18 years of age:

Yes (1) No (2) STOP

10. Gender:

Male (1)
Female (2)

11. Ethnic category *(show the patient 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)

13.

12. What describes your Hispanic, Latino, or Latina origin best *(show the patient Flash Card #1 and ask the respondent 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

13. Racial category *(show the patient Flash Card #2 and ask the respondent to pick the category or categories that describe the patient best; check all that apply)*

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)

14. In what country was the patient born *(check only one):*

Continental US (includes Alaska) or Hawaii	(1)
Other, *(specify):*	(2)

_____
specify

15. Highest educational level achieved by patient *(show the patient Flash Card #3 and ask the respondent to pick the category that describes the patient best; check only one):*

Never attended school	(0)
Kindergarten, pre kindergarten, or younger	(1)
Grades 1 to 5	(2)
Grades 6-8	(3)
Grades 9-11	(4)
Completed high school	(5)
Some college or post high school education or training	(6)
Bachelor's degree or higher	(7)

16. Is the patient currently employed:

(Yes 1) (No 2)

19.

17. What is the patient's current occupation:

_____
specify occupation

18. About how many hours does the patient work each week: ____ ____
hours

19. Which of the following categories best characterizes the patient's occupational history *(show the patient/parent Flash Card #4 and ask the respondent to pick the category that describes the patient best; check only one):*

Never employed	(0)
Laborer	(1)
Clerical	(2)
Professional	(3)
Homemaker	(4)
Other, *(specify):*	(5)

_____
specify

20. Marital status of the patient *(show the patient Flash Card #5 and ask the respondent to pick the category that describes the patient best; check only one):*

Single, never married	(1)
Married or living in marriage-like relationship	(2)
Separated, divorced, or annulled	(3)
Widowed	(4)

21. Combined annual income before taxes of all members of patient's household *(show the patient/parent Flash Card #6 and ask the 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. Previous registration in a NASH CRN study

22. Has the patient ever been assigned an ID number in a NASH CRN study:

(Yes 1) (No 2)

26.

23. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

a. NAFLD Database:	(1)
b. PIVENS:	(1)
c. TONIC:	(1)
d. NAFLD Adult Database 2:	(1)
e. NAFLD Pediatric Database 2:	(1)
f. Other, *(specify):*	(1)

_____
specify

24. ID Number previously assigned to patient *(record patient ID in item 2):*

____ ____ ____ ____

25. Code previously assigned to patient *(record patient code in item 3):*

____ ____ ____

27.

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

FLINT

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.

If Elig 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.

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: r z ____

6. Form & revision: r z 2

7. Study: FLINT 7

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:

Yes (1) No (2)

10.

9. Is the patient's diabetes uncontrolled (HbA1c greater than or equal to 9.5% within the past 60 days):

Yes (1) No (2)

Elig

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:

Yes (1) No (2)

Elig

b. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her *(past and current)* alcohol intake:

Yes (1) No (2)

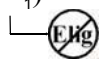
Elig

D. Laboratory test exclusions

11. Hepatic Decompensation

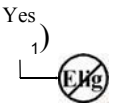
a. Is the patient's serum albumin less than 3.2 g/dL:

(1) Yes (2) No



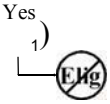
b. Is the patient's INR greater than 1.3:

(1) Yes (2) No



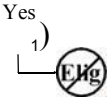
c. Is the patient's direct bilirubin greater than 1.3 mg/dL:

(1) Yes (2) No



d. Does the patient have a history of esophageal varices, ascites, or hepatic encephalopathy:

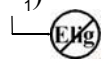
(1) Yes (2) No



12. Other laboratory measures

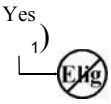
a. Is serum ALT greater than 300 U/L:

(1) Yes (2) No



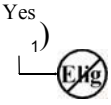
b. Is serum creatinine greater than or equal to 2.0 mg/dL:

(1) Yes (2) No



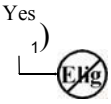
c. Is the platelet count less than 100,000 mm^3:

(1) Yes (2) No



d. Tests are outside time window and clinic chose not to repeat tests:

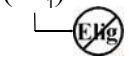
(1) Yes (2) No



E. Medication use exclusions

13. Use of drugs associated with NAFLD for more than 2 weeks in the past 12 months:

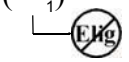
(1) Yes (2) No



F. Other chronic liver disease exclusions

14. Does the patient have ongoing autoimmune liver disease defined by liver histology:

(1) Yes (2) No



15. Does the patient have primary biliary cirrhosis defined by at least two of the following criteria *(check all that apply)*

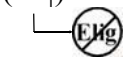
a. Alkaline phosphatase above the upper limit of normal: (1)

b. Presence of antimitochondrial antibody (AMA): (1)

c. Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts: (1)

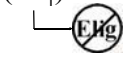
d. Were two criteria checked in 15a-c:

(1) Yes (2) No



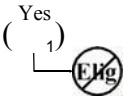
16. Does the patient have known primary sclerosing cholangitis:

(1) Yes (2) No



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:

(1) Yes (2) No



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):*

Yes (1) No (2) Elig

19. Hemochromatosis

a. Does the patient have a history of hemochromatosis:

Yes (1) No (2) Elig

b. Does the patient have iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:

Yes (1) No (2) Elig

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:

Yes (1) No (2) Elig

b. Known bile duct obstruction:

Yes (1) No (2) Elig

c. Suspected or proven liver cancer:

Yes (1) No (2) Elig

d. Hepatitis B (HBsAg):

Yes (1) No (2) Elig

e. Hepatitis C (HCV RNA or anti-HCV):

Yes (1) No (2) Elig

f. Any other type of liver disease other than NASH that warrants exclusion from the trial:

Yes (1) No (2) Elig

G. Liver biopsy exclusions

21. Presence of cirrhosis on liver biopsy:

Yes (1) No (2) Elig

22. Inability to safely undergo a liver biopsy:

Yes (1) No (2) Elig

23. Biopsy out of window and patient chose not to repeat:

Yes (1) No (2) Elig

24. Biopsy inadequate for scoring and patient chose not to repeat:

Yes (1) No (2) Elig

25. Local pathologist did not find borderline or definite steatohepatitis:

Yes (1) No (2) Elig

26. NAFLD activity score (NAS) less than 4 or any subscore (steatosis, ballooning, lobular inflammation) equal to 0:

Yes (1) No (2) Elig

H. Other medical exclusions

27. History of bariatric surgery or plans to have bariatric surgery during the FLINT trial:

Yes (1) No (2) Elig

28. History of biliary diversion:

Yes (1) No (2) Elig

29. Known positivity for HIV infection:

Yes (1) → Elig   No (2)

30. Known active, serious medical disease with a likely life-expectancy of less than 5 years:

Yes (1) → Elig   No (2)

31. Known active substance abuse (inhaled or injected) in the past 12 months:

Yes (1) → Elig   No (2)

32. Participated in an IND trial in the past 30 days:

Yes (1) → Elig   No (2)

33. Other conditions which, in the opinion of the investigator, would impede compliance or hinder completion of the study:

Yes (1) → Elig   No (2)

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):*

Yes (1)   No (2) → Elig

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:

Yes (1) → **44.**   No (* 2)

**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:

Yes (1) → **44.**

No (2)

Task not run because patient is known to be ineligible (3) → **44.**

37. Does the patient feel well today:

Yes (1)   No (* 2) → STOP

**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:

Yes (1) → **42.**   No (2)

39. Is the patient of childbearing potential:

Yes (* 1)   No (2) → **42.**

**Administer pregnancy test.*

40. Is the patient pregnant *(positive pregnancy test on the day of randomization):*

Yes (* 1) → Elig   No (2)

**Go to item 44.*

41. Is the patient currently breast feeding

Yes (*1) No (2)

Elig

**Go to item 44.*

42. In the Study Physician's judgment, is there any reason to exclude the patient from randomization:

Yes (*1) No (2)

Elig

**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):*

Yes (*1) No (†2)

45. Elig

**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: (1)

b. Other reason not covered on this form *(specify):* (1)

_____
specify

L. Administrative information

45. Study Physician PIN: ___ ___ ___

46. Study Physician signature:

_____

47. Clinical Coordinator PIN: ___ ___ ___

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.)

FLINT

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.

A. Center, patient 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: 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:

Yes (1) No (*2) → STOP

** 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 (3)

C. Requirements for screening biopsy

10. Is this visit s:

Yes (1) No (2) → 12.

11. Is the date in item 9a within 90 days of the anticipated date of randomization:

Yes (1) No (*2) → F.Hg

** 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:

(Yes * 1) (No 2)

** If Yes, complete the Liver Tissue Banking (LT) form*

13. What stained slides from the biopsy are available at the clinical center *(check all that apply)*

a. H & E stain: (1)

b. Masson's trichrome stain: (1)

c. Iron stain: (1)

E. Unstained slides to be sent to the DCC

14. Are unstained slides available for sending to the DCC:

(Yes 1) (No 2)

17.

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 ___ ___ 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 3 unstained slides will be sent to the DCC)

17. Are any stained slides to be sent to the DCC:

(Yes 1) (No 2)

25.

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

b. Slide sequence number of Masson's trichrome stain: ___ ___ 81-90

c. Slide sequence number of iron stain: ___ ___ 81-90

d. Slide sequence number of other stain: ___ ___ 81-90

20. Are any stained slides to be returned to the clinic:

(Yes 1) (No 2)

25.

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

b. Slide sequence number: ___ ___ 81-90

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 (1)

At the end of the NASH CRN funding period (2)

24. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department (1)

25.

Other, *(specify):* (2)

_____
name

_____
address

_____
address

_____
address

_____
phone

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.

G. Administrative information

25. Clinical Coordinator PIN: ____ ____ ____

26. Clinical Coordinator signature:

_____

27. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

FLINT

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____
If report not associated with a visit, fill in ''n.''

6. Form & revision: s r 3

7. Study: FLINT 7

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 (2)
Possibly yes (3)
Probably no (4)
15.
Definitely no (5)
15.

12. Is this a serious adverse event:

Yes (1) No (2)
15.

If Yes, then select all the reasons that apply:

a. Severity Grade 4 or 5: (1)

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: (1)

e. Congenital abnormality or birth defect: (1)

13. Is this an unexpected adverse event:

Yes (1) No (2)
15.

14. Reason the adverse event was unexpected:

Not listed in the obeticholic acid investigator brochure (1)

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

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

Yes (*1) No (†2)
STOP

**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 (1)
Followup report (2)

17. Date of serious adverse event onset:

____ ____–____ ____ ____–____ ____
day mon year

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

____ ____–____ ____ ____–____ ____
day mon year

19. Describe the serious adverse event:

20. Medications or supplements other than FLINT study drug in use at the time of serious adverse event:

_____

_____

_____

_____

_____

21. Specify tests/treatments and comorbidities:

_____

_____

_____

_____

_____

22. Was an unscheduled liver biopsy performed:

(Yes *1) (No 2)

**Attach a copy of the institutional pathology report to the SR form.*

23. Did the serious adverse event result in significant sequelae:

(Yes 1) (No 2)

24.

Specify:

_____

_____

_____

_____

24. Short name for serious adverse event *(short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Studies and then click on FLINT):*

_____

_____

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 (*3)

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

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

Resolved (1)

Active (2)

28.

Unknown (3)

28.

27. Date resolved:

____ ____–____ ____ ____–____ ____
day mon year

28. Additional comments on serious adverse event:

_____

_____

_____

_____

E. Administrative information

29. Study Physician PIN: ____ ____ ____

30. Study Physician signature:

_____

31. Clinical Coordinator PIN: ____ ____ ____

32. Clinical Coordinator signature:

_____

33. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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

(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).

FLINT

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of notification of intent to transfer:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____

6. Form & revision: t n 1

7. Study: FLINT 7

B. Last followup visit information

8. Date of last followup visit:

____ ____–____ ____ ____–____ ____
day mon year

9. Visit ID code of last completed followup visit: ____ ____ ____

10. Have cryovial and slide labels been sent to the adopting center:

Yes (1) No (*2)

** Send the cryovial and slide labels to the adopting center.*

C. Enrolling center administrative information

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

12. Clinical coordinator ID: ____ ____ ____

13. Clinical coordinator signature:

_____

D. Adopting center, patient and visit identification

14. Adopting center ID: ____ ____ ____ ____

15. Patient ID *(must be same as in Section A):* ____ ____ ____ ____

16. Patient code: *(must be same as in Section A):* ____ ____ ____

17. Expected date of first followup visit at adopting center:

____ ____–____ ____ ____–____ ____
day mon year

18. Visit ID code for expected first followup visit at adopting center: f ____ ____

Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.

E. Adopting center administrative information

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

20. Clinical coordinator ID: ____ ____ ____

21. Clinical coordinator signature:

_____

Fax form to the DCC. The DCC will key the TN form.

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
BH	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

CyNCh

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.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit *(date patient completed the form)*:

_____ _____ - _____ _____ _____ - _____ _____
day mon year

5. Visit code: **s** _____ _____

6. Form & revision: **a d 1**

7. Study: CyNCh 8

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient (1)
→ **10.**

Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that 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

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)

→ **22.**

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?

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

15. 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
(0)	(1)	(2)	(3)	(4)

16. 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
(0)	(1)	(2)	(3)	(4)

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?

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

18. 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
(0)	(1)	(2)	(3)	(4)

19. 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
(0)	(1)	(2)	(3)	(4)

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

No	Yes, but not in the last year	Yes, during the last year
(0)	(1)	(2)

21. 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
(0)	(1)	(2)

22. Today's date:

_____

Thank you for completing this questionnaire.

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____
if report not associated with a visit, fill in "n"

6. Form & revision: a e 1

7. Study: CyNCh 8

B. Visit interval identification

8. Since the last visit, has the patient had a reportable event:

(Yes 1) (No 2)

33. ____

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:

(Yes 1) (No 2)

11. ____

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:

(Yes 1) (No 2)

12. ____

If Yes, specify health problem and list dates:

_____

_____

C. Patient information

12. Gender:

Male (1)
Female (2)

13. Age at time of event: ____ ____
years

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)
b. Medication related event: (1)
c. Study procedure related event: (1)
d. Severe allergic reaction: (1)
e. Drug interactions: (1)
f. Worsening of a co-morbid illness: (1)
g. Patient reported symptom of hepatotoxicity: (1)
h. Gastrointestinal symptoms: (1)
i. Diabetes: (1)
j. Pregnancy *(patient):* (* 1)
k. Other *(specify):* (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:

_____

_____

_____

_____

_____

_____

For items 18, 19, and 20, please refer to CTCAE v3.0 available at www.nashcrn.com; click on Studies and then CyNCh.

18. Identify body system *(check all that apply)*

a. Auditory/ear: (1)
b. Allergy/immunologic: (1)
c. Ocular/visual: (1)
d. Hepatobiliary/pancreatic: (1)
e. Infection: (1)
f. Constitutional symptoms: (1)
g. Psychiatric: (1)
h. Cardiovascular: (1)
i. Dermatologic/skin: (1)
j. Endocrine/metabolic: (1)
k. Gastrointestinal/digestive: (1)
l. Lymphatic/blood: (1)
m. Musculoskeletal: (1)
n. Neurologic: (1)
o. Pulmonary/respiratory: (1)
p. Renal/genitourinary: (1)
q. Sexual/reproductive: (1)
r. Other *(specify):* (1)

_____
specify other body system

s. None of the above: (1)

19. Short name for event if applicable:

Not applicable (0)

_____

_____

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 (4)
Grade 5 - Death (*5)

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

21. Randomization in CyNCh

a. Has patient been randomized in CyNCh:

Yes (1) No (2)

29. ___

b. Date randomized in CyNCh:

____ ____–____ ____ ____–____ ____
day mon year

22. Is the patient currently receiving the CyNCh study drug:

Yes (1) No (2)

23. Patient's history of treatment with CyNCh study drug

a. How long has patient been on study drug:

_____

b. What daily dose was the patient taking prior to the adverse event:

____ ____ ____
mg/day

c. Have there been any treatment interruptions or restarts:

Yes (1) No (2)

Include stop/restart dates and reasons:

_____

_____

_____

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

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

25. Is this a serious adverse event:

Yes (1) No (2)

26.

If Yes, then select all the reasons that apply:

a. Severity Grade 4 or 5: (1)

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: (1)

e. Congenital anomaly or birth defect: (1)

26. Is this an unexpected adverse event:

Yes (1) No (2)

28.

27. Reason the adverse event was unexpected:

Not listed in the cysteamine bitartrate investigator's 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)

28. Did you select "Yes" for items 24 (definitely, probably, or possibly), 25, and 26:

Yes (*1) No (2)

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

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

Resolved (1)
Active (2)
31.
Unknown (3)
31.

30. Date adverse event resolved:

____ ____–____ ____ ____–____ ____
day mon year

31. What action was taken:

32. Other comments on event:

E. Administrative information

33. Clinical Coordinator PIN: ____ ____ ____

34. Clinical Coordinator signature:

_____

35. Study Physician PIN: ____ ____ ____

36. Study Physician signature:

_____

37. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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.

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 △C is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for CyNCh. If Elig 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.

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: s ____ ____

6. Form & revision: b h 1

7. Study: CyNCh 8

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):*

Yes (*1) No (2)
→ **11.**

**Randomization must be done within 120 days of liver biopsy.*

9. Date of liver biopsy:

____ ____–____ ____ ____–____ ____
day mon year

10. Last day to randomize based on liver biopsy date *(120 days after biopsy; use date calculator 2 on the NASH CRN home page):*

____ ____–____ ____ ____–____ ____
day mon year
→ **12.**

11. Will the patient have a biopsy during screening:

Yes (*1) No (2)
→ Elig

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:

Yes (1) No (2)
→ **19.**

13. Menarche history

a. Has menarche occurred:

Yes (1) No (2)
→ **19.**

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 (4)

15. Is the patient of childbearing potential:

Yes (1) No (2)
→ **19.**

16. Is the patient currently pregnant:

Yes (1) No (2)
→ Elig

17. Is the patient currently breastfeeding:

(Yes *1) C (No 2)

**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:

(Yes 1) Elig (No 2)

D. Medical history *(C 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: (*1)

b. Diabetes type 2: (*1)

**If HbA1c is > 9%, patient is ineligible.*

c. Hepatitis B: Elig (1)

d. Hepatitis C: Elig (1)

e. Autoimmune hepatitis: Elig (1)

f. Autoimmune cholestatic liver disorder (PBC or PSC): C (1)

g. Wilson's disease: Elig (1)

h. Alpha-1-antitrypsin (A1AT) deficiency: Elig (1)

i. Hemochromatosis or iron overload: Elig (1)

j. Drug induced liver disease: Elig (1)

k. Ascites: C (1)

l. Gilbert's syndrome: (1)

m. Esophageal or gastric varices on endoscopy: C (1)

n. Bleeding from varices: Elig (1)

o. Gastrointestinal ulcers or other gastrointestinal bleeding: Elig (1)

p. Biliary diversion: C (1)

q. Metabolic acidosis: C (1)

r. Edema: C (1)

s. Hepatic encephalopathy: Elig (1)

t. Any other evidence of chronic liver disease: C (1)

u. Currently active inflammatory bowel disease: Elig (1)

v. Short bowel syndrome: C (1)

w. Small intestine resection: Elig (1)

x. Renal dysfunction with creatinine clearance < 90 mL/min/m^2: Elig (1)

y. Hemophilia *(bleeding disorder):* Elig (1)

z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)

aa. Endocrine disease *(hormonal abnormality):* (1)

ab. Asthma: (1)

ac. Hepatocellular carcinoma: (1)

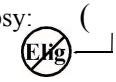
ad. Other malignancy *(cancer):* (1)

ae. Active malignant disease requiring chemotherapy or radiation within the past year: (1)

af. Human immunodeficiency virus (HIV): (1)

ag. Peripheral neuropathy: (1)

ah. Active seizure disorder or epilepsy: (1)



ai. Drug allergies: (1)

aj. Hypothyroidism: (1)

ak. Hypertension: (1)

al. Cerebrovascular disease: (1)

am. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)

an. Pancreatitis: (1)

ao. Cholelithiasis: (1)

ap. Coronary artery disease: (1)

aq. Congestive heart failure: (1)

ar. Myocardial infarction: (1)

as. Unstable arrhythmias: (1)

at. Elevated uric acid such as gout: (1)

au. Kidney disease: (1)

av. Polycystic ovary syndrome: (1)

aw. Sleep apnea: (1)

ax. Dermatologic disorders: (1)

ay. Myopathy: (1)

az. Myositis: (1)

ba. Major depression: (1)

bb. Schizophrenia: (1)

bc. Bipolar disorder: (1)

bd. Obsessive compulsive disorder: (1)

be. Severe anxiety or personality disorder: (1)

bf. Substance abuse: (1)

bg. None of the above: (1)

20. Has the patient ever had bariatric surgery for any of the following *(check all that apply)*

a. Stapling or banding of the stomach: (1)

b. Jejunoileal *(or other intestinal)* bypass: (1)

c. Biliopancreatic diversion: (1)

d. Other bariatric surgery *(specify):* (1)

_____

e. None of the above: (1)

21. Is the patient currently undergoing evaluation for bariatric surgery:

Yes (1) No (2)

22. Has the patient received total parenteral nutrition (TPN) in the past year:

Yes (1) No (2)

23. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

(Yes 1) (No 2)

→ Elig

b. Has the patient ever received any other organ, limb, or bone marrow transplant:

(Yes 1) (No 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): (1)

b. Demeclocycline (Declomycin): (1)

c. Divalproex (Depakote): (1)

d. Doxycycline (Monodox): (1)

e. Isonicotinylhydrazine (INH, Isoniazid, Tubizid): (1)

f. Isotretinoin (Accutane, Amnesteem, Clarvis, or Sotret): (1)

g. Methotrexate (Rheumatrex): (1)

h. Minocycline (Dynacin, Minocin): (1)

i. Oxytetracycline (Terramycin): (1)

j. Tetracycline (Achromycin): (1)

k. Valproate sodium (Depacon): (1)

l. Valproic acid (Depakene): (1)

m. Other known hepatotoxin *(specify):* (1)

_____

n. None of the above: (1)

25. Were any of the items in 24a-m checked:

(Yes * 1) (No 2)

→ C

**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): (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)

27. Were any of the items 26a-k checked:

(Yes * 1) (No 2)

→ C

**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): (1)

b. Fluoxymesterone (Android-F, Halotestin): (1)

c. Methandrostenolone (Dianabol): (1)

d. Methyltestosterone (Android): (1)

e. Nandrolone (Deca-Durabolin, 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)

29. Were any of the items 28a-l checked:

Yes (* 1) → C No (2)

**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:

Yes (1) → Elig No (2)

F. Use of antidiabetic drugs

31. Has the patient used any antidiabetic medications in the past 6 months:

Yes (1) No (2) → 32.

(If yes, check all that apply)

a. Acarbose (Precose): (1)

b. Acetohexamide (Dymelor): (1)

c. Chlorpropamide (Diabinese): (1)

d. Exenatide (Byetta, Bydureon): (1)

e. Glimepiride (Amaryl): (1)

f. Glipizide (Glucotrol, Glucatrol XL): (1)

g. Glyburide (Micronase, DiaBeta, Glynase): (1)

h. Insulin: (1)

i. Metformin (Glucophage, Glucophage XR): (1)

j. Miglitol (Glycet): (1)

k. Nateglinide (Starlix): (1)

l. Pioglitazone (Actos): (1)

m. Repaglinide (Prandin): (1)

n. Rosiglitazone (Avandia): (1)

o. Tolazamide (Tolinase): (1)

p. Tolbutamide (Orinase): (1)

q. Other, *(specify):* (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:

Yes (1) No (2) → **34.**

(If yes, check all that apply)

a. Betaine (Cystadone): (1)

b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)

c. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)

d. S-Adenylmethionine (SAM-e): (1)

e. Milk thistle: (1)

f. Probiotics: (1)

g. Gemfibrozil (Gen-Fibro, Lopid): (1)

h. Vitamin E: (1)

i. Other *(specify):* (1)

_____
specify

33. Were any of the medications/supplements checked in items 32a-i initiated after the screening liver biopsy being used for CyNCh:

Yes (1) → Elig No (2)

34. Has the patient taken any vitamins in the past 6 months:

Yes (1) No (2) → **35.**

(If yes, check all that apply)

a. Vitamin A: (1)

b. Vitamin B (any type): (1)

c. Vitamin C: (1)

d. Vitamin D: (1)

e. Vitamin E: (1)

f. Multivitamin: (1)

g. Other, *(specify):* (1)

_____

H. Use of statins, fibrates, and antiobesity drugs

35. Has the patient taken any lipid lowering medications in the past 6 months:

Yes (1) No (2) → **36.**

(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)

j. Simvastatin (Zocor): (1)

k. Other, *(specify):* (1)

_____

36. Has the patient taken any antiobesity medications in the past 6 months:

Yes (1) No (2)

37.

(If yes, check all that apply)

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)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

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:

Yes (1) No (2)

38.

(If yes, check all that apply)

a. Acetaminophen (Tylenol): (1)

b. Aspirin - 325 mg: (1)

c. Ibuprofen (Advil, Motrin): (1)

d. Naproxen (Aleve, Naprosyn): (1)

e. Other, *(specify):* (1)

_____

f. Other, *(specify):* (1)

_____

38. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 6 months:

Yes (1) No (2)

39.

(If yes, 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)

_____

39. Has the patient taken any cardiovascular/antihypertensive medications in the past 6 months:

(1) Yes (2) No

40.

(If yes, check all that apply)

a. Amlodipine besylate (Norvasc): (1)

b. Aspirin - 81 mg: (1)

c. Atenolol (Tenormin): (1)

d. Benazepril (Lotensin): (1)

e. Captopril (Capoten): (1)

f. Clonidine (Catapres): (1)

g. Digoxin (Lanoxin): (1)

h. Diltiazem (Cardizem): (1)

i. Doxazosin (Cardura): (1)

j. Enalapril (Vasotec): (1)

k. Felodipine (Plendil): (1)

l. Furosemide (Lasix): (1)

m. Hydrochlorothiazide (Esidrix, HydroDIURIL): (1)

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): (1)

s. Nifedipine (Adalat, Procardia): (1)

t. Perhexiline maleate: (1)

u. Propranolol (Inderal): (1)

v. Quinapril (Accupril): (1)

w. Terazosin (Hytrin): (1)

x. Timolol maleate (Blocadren): (1)

y. Valsartan (Diovan): (1)

z. Verapamil (Calan): (1)

aa. Other, *(specify):* (1)

_____

ab. Other, *(specify):* (1)

_____

40. Has the patient taken any allergy or asthma medications in the past 6 months that have not already been reported on this form:

(1) Yes (2) No

41.

(If yes, check all that apply)

a. Albuterol: (1)

b. Beclomethasone dipropionate (Beclovent, Vanceril): (1)

c. Budesonide (Pulmicort, Rhinocort): (1)

d. Fluticasone propionate (Flonase, Flovent): (1)

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

g. Triamcinolone acetonide (Azmacort, Nasacort): (1)

h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

41. Has the patient taken any antipsychotic or antidepressant medications in the past 6 months:

(1) Yes (2) No

42.

(If yes, check all that apply)

a. Aripipazole (Abilify): (1)

b. Buporpion (Wellbutrin): (1)

c. Clomipramine (Anafranil): (1)

d. Escitalopram (Lexapro): (1)

e. Fluoxetine (Prozac): (1)

f. Fluvoxamine (Luvox): (1)

g. Lithium (Eskalith, Lithobid): (1)

h. Quetiapine (Seroquel): (1)

i. Risperidone (Risperdal): (1)

j. Sertraline (Zoloft): (1)

k. Other (specify): (1)

_____

42. Has the patient taken any supplements in the past 6 months that have not already been reported on this form:

Yes (1) No (2)

43.

(If yes, 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)
l. 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)

_____

43. Has patient taken any of the following medications in the past 6 months:

Yes (1) No (2)

44.

(If yes, check all that apply)

a. Isotretinoin (Accutane): (1)
b. Levonorgestrel (Norplant): (1)
c. Levothyroxine (Levoxyl, Synthroid): (1)
d. Liothyronine (Cytomel): (1)
e. Oral contraceptives: (1)
f. Penicillamine (Cuprimine, Depen): (1)
g. Trientine hydrochloride (Syprine): (1)
h. Other, *(specify):* (1)

_____

i. Other, *(specify):* (1)

_____

j. Other, *(specify):* (1)

_____

k. Other, *(specify):* (1)

_____

l. Other, *(specify):* (1)

_____

J. 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

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 identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: b p 2

7. Study: CyNCh 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:

Yes (1) No (2)

**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 NAFLD 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.

9. Date and time of blood draw

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour minute am pm

10. Number of heparin (green-top) tubes: ____

11. Affix matching heparin tube MACO label *(only key NASH ID):*

CyNCh Form BP,
BP Plasma.
Pt: 9999, xyz
Visit vvv
Date:

12. Number of SST serum separator (red-gray top) tubes: ____

13. Attach duplicate SST serum separator tube labels *(only key NASH ID):*

CyNCh Form BP, Serum 1
Pt: 9999, xyz
Visit: vvv
BP
Date:

CyNCh Form BP, Serum 2
Pt: 9999, xyz
Visit: vvv
BP
Date:

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 20 2.0 mL pre-labeled cryovials.

15. Date and time of separation into plasma and serum aliquots

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time of plasma separation:

____ ____ : ____ ____ (1) (2)
hour minute am pm

c. Time of serum separation:

____ ____ : ____ ____ (1) (2)
hour minute am pm

16. Number of aliquots for plasma: ____ ____

17. Number of aliquots for serum: ____ ____

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. Date and time cryovials frozen in -70°C or -20°C

a. Date:

____ ____–____ ____ ____–____ ____
day mon year

b. Time:

____ ____:____ ____ (1) (2)
hour minute am pm

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.

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: c g 1

7. Study: CyNCh 8

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:

Yes (1) No (2)

10.

9. For which study was it collected *(check all that apply):*

a. Database (1)

b. TONIC (1)

c. Database 2 (1)

d. Other, *(specify):* (1)

_____
specify

20.

10. Does the patient/guardian assent/consent to genetic research on NAFLD that is currently planned by the study investigators:

Yes (1) No (2)

11. Does the patient/guardian assent/consent to future genetic research on NAFLD by this study or other study investigators:

Yes (1) No (2)

12. Does the patient/guardian assent/consent to future genetic research not related to NAFLD by this study or other study investigators:

Yes (1) 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 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):*

Yes (1) No (2)

20. ___

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:

Yes (1)

16. ___

No, *(specify):* (2)

_____
specify

20. ___

16. Date and time of blood draw

a. Date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

b. Time:

____ ____ : ____ ____ (1) (2)
hour minute am pm

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

CyNCh

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 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:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: f 7 6

6. Form & revision: c o 1

7. Study: CyNCh 8

B. Database participation

8. Does the patient/parent wish to re-enter or join the NAFLD Database 2:

Yes (1) No (2)

11.

9. Has the patient/parent signed the latest version of the NAFLD Database 2 informed consent:

Yes (1) No (*2)

STOP

** Patient/parent must sign the informed consent*

10. Was the patient enrolled in the NAFLD Database 2 previously:

Yes (*1) No (+2)

** 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 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

c r 2 6. Form and revision

__ 7. Study: **6**=Database 2; **7**=FLINT; **8**=CyNCh

__ __ / __ __ __ / __ __ 8. Date of biopsy

B. Slide sequence number

9. 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 (*Specify*):

D. Histology

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

_____ . . . b. Micrograniulomas seen: **0**=No; **1**=Yes

_____ . . . c. Large lipogranulomas seen: **0**=No; **1**=Yes

_____ . . . d. Amount of portal, chronic inflammation: **0**=None; **1**=Mild; **2**=More than mild

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

_____ . . . e. Pigmented macrophages (*Kupffer cells*): **0**=Rare/absent; **1**=Many

_____ . . . f. Megamitochondria: **0**=Rare/absent; **1**=Many

_____ 16. Mallory-Denk bodies: **0**=Rare/absent; **1**=Many

_____ 17. Glycogen nuclei: **0**=Rare/absent; **1**=Present in patches

_____ 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 (*does not require trichrome*); **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

_____ 22. Is cirrhosis present? **0**=No ➜ **GOTO item 25**; **1**=Yes

_____ 23. Is this cryptogenic cirrhosis: **0**=No ➜ **GOTO item 25**; **1**=Yes

24. Features suggestive of steatohepatitis etiology for cryptogenic cirrhosis:

_____ . . . a. Mallory-Denk bodies (*rule out cholate stasis*): **0**=Absent; **1**=Present

_____ . . . b. Perisinusoidal fibrosis away from septa: **0**=Absent; **1**=Present

_____ . . . c. Hepatocyte ballooning: **0**=Absent; **1**=Present

_____ . . . d. Megamitochondria: **0**=Absent; **1**=Present

_____ . . . e. Other notable findings: **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	Number of Bottles/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
	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 identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

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

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____

6. Form & revision: **d d 1**

7. Study: CyNCh 8

B. Study drug dispensing

8. Which weight group was the patient assigned to at randomization *(check only one)*:

≤65 kg at baseline *(600 mg/day)* (1)

>65 kg - ≤80 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 (1) No (2)

11. ←

10. How many capsules per day has the patient been taking since the last study visit:

_____ _____
(00-11)

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 (1)

Sprinkling the capsule contents into food (2)

Swallowing some and sprinkling some (3)

Other, *(specify)*: (4)

_____

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:

_____
(0-6)

b. Number of capsules to be taken in the evening:

_____
(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 identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form is initiated *(date of notice):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____

6. Form & revision: d r 1

7. Study: CyNCh 8

B. Death information

8. Date of death:

____ ____–____ ____ ____–____ ____
day mon year

9. Source of death report *(check all that apply):*

a. Patient's family: (1)
b. Friend: (1)
c. Health care provider or NASH CRN staff: (1)
d. Newspaper: (1)
e. Funeral parlor/home: (1)
f. Medical record: (1)
g. Medical examiner: (1)
h. Coroner: (1)
i. Other *(specify):* (1)

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

11. Cause of death
(Study Physician: use whatever knowledge you have and your best medical judgment to best characterize the cause of death; check only one):

Heart disease (1)
Stroke (2)
Liver disease (3)
Malignancy (4)
Other *(specify):* (5)

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

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 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: ____ ____ ____

6. Form & revision: f h 1

7. Study: CyNCh 8

B. Interval identification

8. Date of last Follow-up Medical History form *(if this is visit f04, then date of s):*

____ ____–____ ____ ____–____ ____
day mon year

9. Visit code of last Follow-up Medical History form *(if this is visit f04, then s):*

____ ____ ____

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

Yes (*1) No (2)

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

C. Use of effective birth control

11. Is the patient female:

Yes (1) No (2)

14.

12. Has menarche occurred:

Yes (1) No (2)

14.

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 (0)

17.

Monthly or less (1)
Two to four times a month (2)
Two to three times a week (3)
Four or more times a week (4)

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. Recent medical history

17. Has the patient been diagnosed with any of the following since the last visit *(check all that apply; source of information can be interview and/or chart review)*

a. Diabetes type 1: (1)
b. Diabetes type 2: (1)
c. Hepatitis B: (1)
d. Hepatitis C: (1)
e. Autoimmune hepatitis: (1)
f. Autoimmune cholestatic liver disorder (PBC or PSC): (1)
g. Wilson's disease: (1)
h. Alpha-1-antitrypsin (A1AT) deficiency: (1)
i. Hemochromatosis or iron overload: (1)
j. Drug induced liver disease: (1)
k. Ascites: (1)
l. Gilbert's syndrome: (1)
m. Esophageal or gastric varices on endoscopy: (1)
n. Bleeding from varices: (1)
o. Gastrointestinal ulcers or other gastrointestinal bleeding: (1)
p. Biliary diversion: (1)
q. Metabolic acidosis: (1)
r. Edema: (1)
s. Hepatic encephalopathy: (1)
t. Any other chronic liver disease: (1)
u. Inflammatory bowel disease: (1)
v. Short bowel syndrome: (1)
w. Small intestine resection: (1)
x. Hemophilia *(bleeding disorder):* (1)
y. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)
z. Endocrine disease *(hormonal abnormality):* (1)
aa. Asthma: (1)
ab. Hepatocellular carcinoma: (1)
ac. Other malignancy *(cancer):* (1)
ad. Human immunodeficiency virus (HIV): (1)
ae. Peripheral neuropathy: (1)
af. Active seizure disorder or epilepsy: (1)
ag. Drug allergies: (1)
ah. Hypothyroidism: (1)
ai. Hypertension: (1)
aj. Cerebrovascular disease: (1)
ak. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)
al. Pancreatitis: (1)
am. Cholelithiasis: (1)
an. Coronary artery disease: (1)
ao. Congestive heart failure: (1)
ap. Myocardial infarction: (1)
aq. Unstable arrhythmias: (1)
ar. Elevated uric acid such as gout: (1)
as. Kidney disease: (1)
at. Polycystic ovary syndrome: (1)
au. Sleep apnea: (1)
av. Dermatologic disorders: (1)
aw. Myopathy: (1)
ax. Myositis: (1)
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)

18. Since the last visit, has the patient had bariatric surgery *(check all that apply)*

a. Stapling or banding of the stomach: (1)

b. Jejunoileal *(or other intestinal)* bypass: (1)

c. Biliopancreatic diversion: (1)

d. Other bariatric surgery *(specify):* (1)

_____

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 (1) No (2) **20.**

(If yes, check all that apply)

a. Amiodarone (Pacerone): (1)

b. Demeclocycline (Declomycin): (1)

c. Divalproex (Depakote): (1)

d. Doxycycline (Monodox): (1)

e. Isonicotinylhydrazine (INH, Isoniazid): (1)

f. Isotretinoin (Accutane): (1)

g. Methotrexate (Rheumatrex): (1)

h. Minocycline (Dynacin, Minocin): (1)

i. Oxytetracycline (Terramycin): (1)

j. Tetracycline (Achromycin): (1)

k. Valproate sodium (Depacon): (1)

l. Valproic acid (Depakene): (1)

m. Other known hepatotoxin *(specify):* (1)

_____

20. Since the last visit, has the patient taken any systemic glucocorticoids:

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

(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): (1)

j. Other, *(specify):* (1)

_____

21. Since the last visit, has the patient taken any anabolic steroids or tamoxifen:

Yes (1) No (2) **22.**

(If yes, 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, 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)

_____

G. Use of antidiabetic drugs

22. Since the last visit, has the patient used any antidiabetic medications:

(Yes 1) (No 2) → **23.**

(If yes, check all that apply)

a. Acarbose (Precose): (1)
b. Acetohexamide (Dymelor): (1)
c. Chlorpropamide (Diabinese): (1)
d. Exenatide (Byetta, Bydureon): (1)
e. Glimepiride (Amaryl): (1)
f. Glipizide (Glucotrol): (1)
g. Glyburide (Micronase): (1)
h. Insulin: (1)
i. Metformin (Glucophage): (1)
j. Miglitol (Glycet): (1)
k. Nateglinide (Starlix): (1)
l. Pioglitazone (Actos): (1)
m. Repaglinide (Prandin): (1)
n. Rosiglitazone (Avandia): (1)
o. Tolazamide (Tolinase): (1)
p. Tolbutamide (Orinase): (1)
q. Other, *(specify):* (1)

_____

H. Use of supplements, vitamins, and other drugs

23. Since the last visit, has the patient taken any of the following supplements/drugs:

(Yes 1) (No 2) → **24.**

(If yes, check all that apply)

a. Betaine (Cystadone): (1)
b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
c. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
d. S-Adenylmethionine (SAM-e): (1)
e. Milk thistle: (1)
f. Probiotics: (1)
g. Gemfibrozil (Gen-Fibro, Lopid): (1)
h. Vitamin E: (1)
i. Vitamin A: (1)
j. Vitamin B (any type): (1)
k. Vitamin C: (1)
l. Vitamin D: (1)
m. Multivitamin: (1)
n. Other *(specify):* (1)

_____
specify

I. Use of statins, fibrates, and antiobesity drugs

24. Since the last visit, has the patient taken any lipid lowering medications:

(1) Yes (2) No

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)

j. Simvastatin (Zocor): (1)

k. Other, *(specify):* (1)

_____

25. Since the last visit, has the patient taken any antiobesity medications:

(1) Yes (2) No

26.

(If yes, check all that apply)

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)

h. Other, *(specify):* (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:

(1) Yes (2) No

27.

(If yes, 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)

_____

27. Since the last visit, has the patient taken any cardiovascular/antihypertensive medications:

Yes (1) 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)
l. 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)
y. Verapamil (Calan): (1)
z. Other, *(specify):* (1)

_____

28. Since the last visit, has the patient taken any antipsychotic or antidepressant medications:

Yes (1) No (2)

29. ___

(If yes, check all that apply)

a. Aripipazole (Abilify): (1)
b. Buporpion (Wellbutrin): (1)
c. Clomipramine (Anafranil): (1)
d. Escitalopram (Lexapro): (1)
e. Fluoxetine (Prozac): (1)
f. Fluvoxamine (Luvox): (1)
g. Lithium (Eskalith, Lithobid): (1)
h. Quetiapine (Seroquel): (1)
i. Risperidone (Risperdal): (1)
j. Sertraline (Zoloft): (1)
k. Other (specify): (1)

_____

K. Administrative information

29. Study Physician PIN: ___ ___ ___

30. Study Physician signature:

_____

31. Clinical Coordinator PIN: ___ ___ ___

32. Clinical Coordinator signature:

_____

33. Date form reviewed:

___ ___–___ ___ ___–___ ___
day mon year

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 Elig is checked for any item, the patient is not eligible for CyNCh and the form should not be keyed. If c 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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: h f 1

7. Study: CyNCh 8

B. Biopsy information

8. Date this biopsy was performed *(obtained from surgical pathology report):*

____ ____–____ ____ ____–____ ____
day mon year

9. What slides are to be used in this evaluation *(check all that apply)*

a. H & E: (1)
b. Masson's trichrome: (1)
c. Iron: (1)

10. Biopsy length: ____ ____
mm

C. NASH evaluation (use H & E and Masson's trichrome slides only)

11. Steatosis *(assume macro, e.g., large and small droplet)*

a. Grade:

< 5% (0) Elig
5-33% (1)
34-66% (2)
> 66% (3)

b. Location:

Zone 3 (0)
Zone 1 (1)
Azonal (2)
Panacinar (3)

12. Fibrosis stage *(Masson's trichrome stain)*

0: None (0)
1a: Zone 3, perisinusoidal (requires trichome) (1)
1b: Zone 3, perisinusoidal (easily seen on H & E) (2)
1c: Portal/periportal only (3)
2: Zone 3 and periportal, any combination (4)
3: Bridging (5)
4: Cirrhosis (6)

13. Inflammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

0 (0)
< 2 / 20x mag (1)
2-4 / 20x mag (2)
> 4 / 20x mag (3)

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:

Not NAFLD (0) F.Hg
NAFLD, not NASH (1)
Suspicious/borderline/indeterminate (2)
Yes, definite (3)

D. Exclusion of other liver disease

16. Is there evidence of primary biliary cirrhosis:

Yes (* 1) C No (2)

** Caution: Primary biliary cirrhosis is exclusionary*

17. Is there evidence of Wilson's disease:

Yes (* 1) C No (2)

** Caution: Wilson's disease is exclusionary*

18. Features of chronic cholestatic liver disease *(check all that apply)*

a. Bile duct loss/infiltration/sclerosis: (* 1) C
b. Florid duct lesions: (1)
c. Cholate stasis: (1)
d. Copper deposition: (1)
e. Other *(specify):* (1)

_____

f. None: (1)

** 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: (1)
b. Inflammation suggestive of AIH, HCV: (* 1) C
c. Pigment suggestive of HH: (* 1) C
d. Globules suggestive of A1AT: (* 1) C
e. Hepatocellular changes suggestive of HBV: (* 1) C
f. Granulomas suggestive of sarcoid, PBC, infection: (* 1) C
g. Other *(specify):* (1)

_____

h. None: (1)

** 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: Yes (1) No (2)

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

CyNCh 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.

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: **l p 1**

7. Study: CyNCh 8

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the questionnaire completed:

Self-administered by patient/parent (1)
→ **10.**

Interview in English (2)
Interview with translator (3)

9. Who was the respondent *(check all that 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

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
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 affects you *(choose only one)*:

Circle one

I feel normal and am not tired **(If this is how you feel, please circle "1" and go 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 2
At least part of several days a week 3
At least part of one day a week 4
Not as much as above 5

15. Are you tired *(choose only one)*:

When you wake up in the morning 1
Or does it come on with the day 2
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
No 2

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 (LNG) is checked for any item, then the form should not be keyed.

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: l r 1

7. Study: CyNCh 8

B. Hematology

Required at all visits.

8. Date of blood draw for complete blood 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).

9. Hemoglobin: ____ ____ • ____ ____
g/dL

If hemoglobin < 10 g/dL at screening, patient is ineligible.

10. Hematocrit: ____ ____ • ____ ____
%

11. Mean corpuscular volume (MCV):

____ ____ ____
fL

12. White blood cell values

a. White blood cell count (WBC):

____ ____ • ____
10^3 cells/ µL or 10^9 cells/L

If WBC < 3.5 10^3 cells/mm^3 at screening, patient is ineligible.

b. Neutrophils: ____ ____ ____ ____
cells/ µL

If neutrophils < 1500 cells/mm^3 at screening, patient is ineligible.

c. Lymphocytes: ____ ____ ____ ____
cells/ µL

d. Monocytes: ____ ____ ____ ____
cells/ µL

e. Eosinophils: ____ ____ ____ ____
cells/ µL

f. Basophils: ____ ____ ____ ____
cells/ µL

13. Platelet count:

____ ____ ____,____ ____ ____
cells/mm^3

If platelets < 130,000 cells/mm^3 (mm^3 = µL) at screening, patient is ineligible.

C. Chemistries

Required at visits s, f24, f52, and f76.

14. Is metabolic panel required at this visit:

(Yes 1) (No 2)

24.

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: ____ ____ ____ mEq/L

17. Potassium: ____ ____ • ____ mEq/L

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:

____ ____–____ ____ ____–____ ____
day mon year

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): ____ ____ • ____ sec

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:

(Yes 1) (No 2)

30.

28. Date of blood draw for HbA1c:

____ ____–____ ____ ____–____ ____
day mon year

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):*

____ ____ • ____ %

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: ____ ____ ____
U/L

35. Alkaline phosphatase ____ ____ ____
U/L

a. Upper limit of normal: ____ ____ ____
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:

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

42. ⌊

40. Was participant fasting for at least 8 hours prior to blood draw:

( ) Yes (1) ( ) No (*2)

**12 hour fasting is preferred, but will accept non-fasting 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: ____ ____ ____ ____
mg/dL

b. Total cholesterol: ____ ____ ____
mg/dL

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:

(Yes 1) (No 2)

45.

43. Was participant fasting for at least 8 hours prior to blood draw:

(Yes 1) (No * 2)

45.

**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 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

b. Serum insulin: ____ ____ ____ • ____ ____
µU/mL

I. Pregnancy test

Required at all study visits, if applicable.

45. Is pregnancy test applicable:

(Yes 1) (No 2)

48.

46. Date of urine collection (or blood draw):

____ ____–____ ____ ____–____ ____
day mon year

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 (2)

J. Eligibility check

48. Is this the screening visit:

(Yes 1) (No 2)

50.

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:

(Yes 1) (No 2)

Elig

K. Administrative information

50. Study Physician PIN: ____ ____ ____

51. Study Physician signature:

_____

52. Clinical Coordinator PIN: ____ ____ ____

53. Clinical Coordinator signature:

_____

54. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

CyNCh

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 EHg is checked for any item the patient is not eligible for the CyNCh trial. If △c is checked for an item and the Study Physician agrees with the diagnosis, the patient is ineligible for CyNCh.

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: s ____ ____

6. Form & revision: 1 s 2

7. Study: CyNCh 8

B. Screening etiologic tests

8. Date of blood draw for serological assays to exclude viral causes of chronic liver disease:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 2 years prior to screening.

a. Hepatitis B surface antigen (HBsAg):
Positive (1) EHg
Negative (2)

b. Hepatitis C antibody (anti-HCV) *(indicate result as negative if EIA is positive but RIBA is negative):*
Positive (1) EHg
Negative (2)

c. Hepatitis C virus RNA (HCV RNA):
Positive (1) EHg
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 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/ ____ ____ ____ ____

b. Units: ____ ____ • ____
mg/dL

11. Is ANA titer greater than 1:80

Yes (* 1) No (2)
C

** Check Liver Biopsy Histology Findings Form for autoimmune liver disease.*

12. Date of blood draw for anti-smooth muscle antibody (ASMA):

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 2 years prior to screening.

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):

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____
mg/dL

14. Date of blood draw for anti-mitochondrial antibody (AMA):

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 2 years prior to screening.

15. Anti-mitochondrial antibody (AMA):

Positive (* 1)
Negative (2)
17.
Not available (3)
17.

** If positive AMA value, complete either a or b depending on laboratory results.*

a. Titer (record only the denominator):

1/ ____ ____ ____ ____

b. Units: ____ ____ • ____
mg/dL

16. Is AMA titer greater than 1:80

Yes (* 1) No (2)
C

** 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 is greater than 2 years prior to screening.

18. Ceruloplasmin ____ ____ • ____
mg/dL

a. Lower limit of normal: ____ ____ • ____
mg/dL

b. Is ceruloplasmin below the lower limit of normal:

Yes (* 1) No (2)
C

** 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): ____ ____ ____ mg/dL

a. Lower limit of normal: ____ ____ ____ mg/dL

21. A1AT phenotype/genotype

a. SZ phenotype/genotype:

Yes (1)
No (2)
Unknown (3)

b. ZZ phenotype/genotype:

Yes (1)
No (2)
Unknown (3)

22. Is A1AT deficiency a contributor to liver disease (physician judgment):

Yes (1) No (2)

Elig

F. Iron

23. Date of blood draw for iron overload screening:

____ ____–____ ____ ____–____ ____
day mon year

Repeat if date is greater than 2 years prior to screening.

a. Serum iron: ____ ____ ____ µg/dL

b. Total Iron Binding Capacity: ____ ____ ____ µg/dL

c. Ferritin: ____ ____ ____ ____ ng/mL

24. Is hepatic iron index available:

Yes (1) No (2)

26.

25. Hepatic iron index: ____ • ____ µmol/g/year

G. Administrative information

26. Study Physician PIN: ____ ____ ____

27. Study Physician signature:

_____

28. Clinic Coordinator PIN: ____ ____ ____

29. Clinic Coordinator signature:

_____

30. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

CyNCh

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code *(s or f52):* ____ ____ ____

6. Form & revision: l t 1

7. Study: CyNCh 8

B. Liver biopsy/RNA*later*® Solution storage procedures

8. Date of biopsy:

____ ____–____ ____ ____–____ ____
day mon year

9. Was the liver tissue obtained from a needle core biopsy *(as opposed to a wedge biopsy):*

Yes (1) No (2)

10. Was liver tissue placed in RNA*later*® Solution preferably within 1 minute, but no more than 5 minutes after biopsy:

Yes (1) No (* 2)

13.

* *Discard liver tissue*

11. Was liver tissue refrigerated at 4° C overnight, then transferred to freezer for storage:

Yes (1) No (2)

12.

a. If no, describe conditions of local storage:

_____

_____

C. Cryovial label

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):*

D. Administrative information

13. Clinical Coordinator PIN: ____ ____ ____

14. Clinical Coordinator signature:

_____

15. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

CyNCh

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) Emptied 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.

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: CyNCh 8

8. Is CyNCh MRI protocol currently in use at your center:

Yes (1) No (2)

16.

B. MRI results and information

9. Was an MRI performed:

Yes (1) No (*2)

11.

** 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: (1)

b. Patient was not fasting: (1)

c. Patient suffers from extreme claustrophobia: (1)

d. Patients weight or girth exceeds MRI scanner capabilities: (1)

e. Other *(specify):* (1)

_____

16.

11. Technician name:

_____
print name

12. Date and time of MRI:

____ ____–____ ____ ____–____ ____
day mon year

a. Time:

____ ____ : ____ ____ (1) am (2) pm
hour minute

13. 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

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

CyNCh

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: f ____ ____

6. Form & revision: m v 1

7. Study: CyNCh 8

B. Reason for completion of this form

8. Was the entire visit missed:

(Yes 1) (No 2)

11.

C. Missed visit information

9. Reason for missed visit *(check all that apply)*

a. Patient was ill: (1)

b. Patient was temporarily away from area: (1)

c. Patient refused to return: (1)

d. Patient has permanently moved from the area: (1)

e. Unable to contact patient: (1)

f. Other *(specify):* (1)

_____
specify

10. Steps taken to avoid missing the visit *(check all that apply)*

a. Telephoned patient: (1)

b. Mailed reminder card: (1)

c. Other *(specify):* (1)

_____
specify

14.

D. Missed form information

11. Check form(s) not completed *(check all that apply)*

a. Blood Processing for Plasma and Serum (BP): (1)

b. Follow-up Medical History (FH): (1)

c. Symptoms of Liver Disease (LP): (1)

d. Laboratory Results - Tests Done During Screening and Follow-up (LR): (1)

e. Liver Tissue Banking (LT): (1)

f. Nutrition Data Documentation for NDSR (ND): (1)

g. Physical Examination (PE): (1)

h. Focused Physical Examination (PF): (1)

i. Parent Report for Teens (13-17) (PQ): (1)

j. Pediatric QOL: Parent Report for Child (8-12) (PR): (1)

k. Pediatric QOL: Child Report (PW): (1)

l. Pediatric QOL: Teen Report (PY): (1)

m. Study Drug Dispensing and Return (RD): (1)

n. Liver Biopsy Materials Documentation (SD): (1)

o. MRI Consent and Report Form (MR): (1)

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. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

CyNCh

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form initiated *(cannot precede the date of the first diet recall):*

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: n d 2

7. Study: CyNCh 8

B. Administration of food recall #1

8. Date of 24-hour food recall #1:

____ ____–____ ____ ____–____ ____
day mon year

9. How was the NDS-R food recall completed *(you must check at least three)*

a. Interview in English: (1)
b. Interview with translator: (1)
(check a or b or both)
c. Interview in person: (1)
d. Interview by phone: (1)
(check either c or d)
e. Administered by dietician: (1)
f. Administered by Clinical Coordinator: (1)
g. Administered by other *(specify):* (1)
(check either e, f, or g)

_____
specify

10. Who was the respondent *(check all that 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

11. NDS-R record properties report

a. Energy: ____ ____ ____ ____
kilocalories

b. Total fat: ____ ____ ____ • ____
grams

c. Total saturated fatty acids (SFA):
____ ____ ____ • ____
grams

d. Total carbohydrates:
____ ____ ____ • ____
grams

e. Total sugars: ____ ____ ____ • ____
grams

f. Total protein: ____ ____ ____ • ____
grams

C. Administration of food recall #2

12. Date of 24-hour food recall #2:

____ ____–____ ____ ____–____ ____
day mon year

13. How was the NDS-R food recall completed *(you must check at least three)*

a. Interview in English: (1)

b. Interview with translator: (1)
(check a or b or both)

c. Interview in person: (1)

d. Interview by phone: (1)
(check either c or d)

e. Administered by dietician: (1)

f. Administered by Clinical Coordinator: (1)

g. Administered by other *(specify):* (1)
(check either e, f, or g)

_____
specify

14. Who was the respondent *(check all that 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

15. NDS-R record properties report

a. Energy: ____ ____ ____ ____
kilocalories

b. Total fat: ____ ____ ____ • ____
grams

c. Total saturated fatty acids (SFA):
____ ____ ____ • ____
grams

d. Total carbohydrates:
____ ____ ____ • ____
grams

e. Total sugars: ____ ____ ____ • ____
grams

f. Total protein: ____ ____ ____ • ____
grams

D. Administration of food recall #3

16. Date of 24-hour food recall #3:

____ ____–____ ____ ____–____ ____
day mon year

17. How was the NDS-R food recall completed *(you must check at least three)*

a. Interview in English: (1)

b. Interview with translator: (1)
(check a or b or both)

c. Interview in person: (1)

d. Interview by phone: (1)
(check either c or d)

e. Administered by dietician: (1)

f. Administered by Clinical Coordinator: (1)

g. Administered by other *(specify):* (1)
(check either e, f, or g)

_____
specify

18. Who was the respondent *(check all that 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

19. NDS-R record properties report

a. Energy: ____ ____ ____ ____
kilocalories

b. Total fat: ____ ____ ____ • ____
grams

c. Total saturated fatty acids (SFA):
____ ____ ____ • ____
grams

d. Total carbohydrates:
____ ____ ____ • ____
grams

e. Total sugars: ____ ____ ____ • ____
grams

f. Total protein: ____ ____ ____ • ____
grams

D. Administrative information

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 Report for each 24-hour recall to this form.

CyNCh

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: p e 1

7. Study: CyNCh 8

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement:

____ ____ ____ • ____

b. Weight, 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
waist circumference

c. Units:

Inches (1)
Centimeters (2)

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)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
hip circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
hip circumference

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(Oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:

Fahrenheit (1)
Centigrade (2)

13. Blood pressure

a. Systolic: ____ ____ ____
mmHg

b. Diastolic: ____ ____ ____
mmHg

14. Resting radial pulse: ____ ____ ____
beats/minute

15. Respiratory rate: ____ ____
breaths/minute

C. Examination findings

16. Skin:

Normal (1)
Abnormal (2)
19.

17. Acanthosis nigricans *(check only one):*

Absent *(not detectable on close inspection)* (0)
Present *(clearly present on close inspection, not visible to casual observer, extent not measurable)* (1)
Mild *(limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth)* (2)
Moderate *(extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front)* (3)
Severe *(extending anteriorly, > 6 inches in breadth, visible from front)* (4)

18. Other skin abnormality *(check all that apply)*

a. Jaundice: (1)
b. Palmar erythema: (1)
c. Spider angiomata: (1)
d. Striae: (1)
e. Skin lesions: (1)
f. Other *(specify):* (1)

_____

g. None of the above: (1)

19. Head, eyes, ears, nose, throat:

Normal (1)
Abnormal (2)
20.

_____
specify abnormality

20. Neck:

Normal (1)
Abnormal (2)
21.

_____
specify abnormality

21. Lymphatic:

Normal (1)
Abnormal (2)
22.

_____
specify abnormality

22. Chest and lungs:

Normal (1)
Abnormal (2)
23.

specify

23. Heart:

Normal (1)
Abnormal (2)
24.

specify abnormality

24. Abdomen:

Normal (1)
Abnormal (2)
26.

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

a. Ascites: (1)
b. Obese: (1)
c. Hepatomegaly: (1)
(if checked, span from right midclavicular line):

___ ___ • ___
cm

d. Splenomegaly: (1)
e. Other *(specify):* (1)

26. Extremities:

Normal (1)
Abnormal (2)
28.

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

a. Contractures: (1)
b. Joint hyperextension: (1)
c. Muscle wasting: (1)
d. Palmar erythema: (1)
e. Pedal edema: (1)
f. Other *(specify):* (1)

specify

28. Nervous 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 (1) 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 (2)
EHg

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

CyNCh

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 visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____ – ____ ____ ____ – ____ ____
day mon year

5. Visit code: ____ ____ ____

6. Form & revision: p f 1

7. Study: CyNCh 8

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:
Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:
Pounds (1)
Kilograms (2)

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)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:
Inches (1)
Centimeters (2)

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)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:
Inches (1)
Centimeters (2)

12. Temperature *(oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:
Fahrenheit: (1)
Centigrade: (2)

13. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

14. Resting radial pulse: ___ ___ ___ beats/minute

15. Respiratory rate: ___ ___ breaths/minute

C. Liver signs

16. Liver and spleen:

Normal (1)

18. ___

Abnormal (2)

17. Abnormality *(check all that apply)*

a. Ascites: (1)

b. Asterixis: (1)

c. Contractures: (1)

d. Fetor: (1)

e. Hepatomegaly: (1)

If Yes, span from right midclavicular line:

___ ___ • ___ cm

f. Jaundice: (1)

g. Muscle wasting: (1)

h. Palmar erythema: (1)

i. Pedal edema: (1)

j. Spider angiomata: (1)

k. Splenomegaly: (1)

l. Other, *(specify):* (1)

_____
specify abnormality

D. Administrative information

18. Study Physician ID: ___ ___ ___

19. Study Physician signature:

_____

20. Clinical Coordinator ID: ___ ___ ___

21. Clinical Coordinator signature:

_____

22. Date form reviewed:

___ ___–___ ___ ___–___ ___
day mon year

CyNCh

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____

6. Form & revision: **p q 1**

7. Study: CyNCh 8

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

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

SOCIAL 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

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. 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.

CyNCh

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____

6. Form & revision: **p r 1**

7. Study: CyNCh 8

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

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

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

SOCIAL 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

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. 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.

CyNCh

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____

6. Form & revision: **p w 1**

7. Study: CyNCh 8

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day 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...)*	**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

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.

CyNCh

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 re-attached 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

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date form completed:

_____ _____-_____ _____ _____-_____ _____
day mon year

5. Visit code: _____ _____ _____

6. Form & revision: **p y 1**

7. Study: CyNCh 8

B. Administrative information

(To be completed by Clinical Coordinator after survey is completed.)

8. How was the Pediatric Quality of Life questionnaire completed:

Self-administered in English (1)
Self-administered in Spanish (2)
Interview in English (3)
Interview in Spanish (4)

9. Clinical Coordinator
a. PIN: _____ _____ _____
b. Signature:

_____

10. Date form reviewed:

_____ _____-_____ _____ _____-_____ _____
day mon year

Affix label here

Patient ID: __ __ __ __

Patient code: __ __ __

Visit code: __ __ __

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

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 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

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.

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: r c 1

7. Study: CyNCh 8

B. CyNCh participation

8. Date in item 4 of original CyNCh RG form:

____ ____–____ ____ ____–____ ____
day mon year

C. Administrative information

9. Clinical Coordinator PIN: ____ ____ ____

10. Clinical Coordinator signature:

_____

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

CyNCh

RD – Study Drug Dispensing and Return

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:	1 capsule twice daily (150 mg/day)
	Week 2:	2 capsules twice daily (300 mg/day)
	Week 3:	3 capsules twice daily (450 mg/day)
	Weeks 4-52:	4 capsules twice daily (600 mg/day)
>65-80 kg at baseline	Week 1:	2 capsules twice daily (300 mg/day)
	Week 2:	3 capsules twice daily (450 mg/day)
	Week 3:	4 capsules twice daily (600 mg/day)
	Weeks 4-52:	5 capsules twice daily (750 mg/day
>80 kg at baseline	Week 1:	3 capsules twice daily (450 mg/day)
	Week 2:	4 capsules twice daily (600 mg/day)
	Week 3:	5 capsules twice daily (750 mg/day)
	Weeks 4-52:	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
	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

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: r d 1

7. Study: CyNCh 8

B. Study drug dispensing

8. Is this a second form for returning additional drug bottles at this visit:

Yes (* 1) No (2)

→ **24.**

* *Key first form before this form.*

9. Will study drug be dispensed today:

Yes (1) No (2)

→ **11.**

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: (1)
- **d.** Other *(specify)*: (1)

_____
specify

→ **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*

16. *Affix label here*

17. *Affix label here*

18. *Affix label here*

19. *Affix label here*

20. *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	(1)
Mail	(2)
Other *(specify)*	(3)

_____
specify

C. Study drug return

24. Were any bottles returned at this visit:

Yes (1) No (2)

39. ◄

25. Number of bottles returned *(if more than 12 bottles are returned, complete a second RD form)*:

___ ___
(01-12)

	a. Bottle No.	b. Number of capsules returned
26.	___ ___ ___ ___	___ ___ ___ (000-150)
27.	___ ___ ___ ___	___ ___ ___ (000-150)
28.	___ ___ ___ ___	___ ___ ___ (000-150)
29.	___ ___ ___ ___	___ ___ ___ (000-150)
30.	___ ___ ___ ___	___ ___ ___ (000-150)
31.	___ ___ ___ ___	___ ___ ___ (000-150)
32.	___ ___ ___ ___	___ ___ ___ (000-150)
33.	___ ___ ___ ___	___ ___ ___ (000-150)
34.	___ ___ ___ ___	___ ___ ___ (000-150)
35.	___ ___ ___ ___	___ ___ ___ (000-150)
36.	___ ___ ___ ___	___ ___ ___ (000-150)
37.	___ ___ ___ ___	___ ___ ___ (000-150)

D. Remaining bottles

38. Are any additional bottles being returned:

Yes (* 1) No (2)

**If yes, complete a second RD form using visit code "n."*

IMPORTANT: You must enter this form into the data system **within 48 hours** of dispensing study drug to the participant.

E. 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

CyNCh

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 Elig is checked for any item, the patient is not eligible for CyNCh and the form should not be keyed.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: s ____ ____

6. Form & revision: r g 1

7. Study: CyNCh 8

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:

Yes (1) No (2) → STOP

9. Has the patient (or patient's guardian) signed the CyNCh informed consent statement:

Yes (1) No (2) → STOP

10. Has the patient signed the CyNCh informed assent statement:

Yes (1)
No (2) → STOP
Not using assent (3)
Not using assent for this age child (4)

C. Information about patient

11. Date of birth:

____ ____–____ ____ ____–____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

12. Age at last birthday: ____ ____
years

13. Is the patient's age at least 8 years old and less than 18 years:

Yes (1) No (2) → Elig

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 Hispanic, Latino, or Latina origin best *(show the patient/guardian Flash Card #1 and ask the respondent to pick the subcategory that best describes the patient's 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

17. Racial category *(show the patient/guardian Flash Card #2 and ask the respondent to pick the category or categories that describe the patient best; check all that apply)*

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/guardian refused:	(1)

18. In what country was the patient born *(check only one):*

Continental US (includes Alaska) or Hawaii	(1)
Other, *(specify):*	(2)

_____
specify

19. Patient's current grade level in school (or home school) *(show the patient/guardian Flash Card #3 and ask the respondent to pick the category that describes the patient best; if summer time, report grade entering in the fall; check only one):*

Grades 1 to 5	(1)
Grades 6-8	(2)
Grades 9-12	(3)
Other, *(specify):*	(4)

_____
specify

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)
$15,000 - $29,999	(2)
$30,000 - $49,999	(3)
$50,000 or more	(4)

D. Previous registration in a NASH CRN study

21. Has the patient ever been assigned an ID number in a NASH CRN study:

Yes (1) No (2)

25. ⌊

22. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

a. NAFLD Database:	(1)
b. TONIC:	(1)
c. NAFLD Pediatric Database 2:	(1)
d. Other, *(specify):*	(1)

_____
specify

23. ID Number previously assigned to patient *(record patient ID in item 2):*

____ ____ ____ ____

24. Code previously assigned to patient *(record patient code in item 3):*

____ ____ ____

26. ⌊

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 previously registered in a NASH CRN study, a new ID number should not be assigned.)

25. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####,zzz

F. Administrative information

26. Clinical Coordinator PIN: ____ ____ ____

27. Clinical Coordinator signature:

_____

28. Date form reviewed:

____ ____–____ ____ ____–____ ____
day 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 Elig 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 "**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: r z ____

6. Form & revision: r z 2

7. Study: CyNCh 8

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:

Yes (1) No (2)

10.

9. Is the patient's diabetes poorly controlled (HbA1c greater than 9% within the past 90 days):

Yes (1) No (2)

Elig

C. Alcohol use exclusions

10. Does the patient have a history of significant alcohol intake:

Yes (1) No (2)

Elig

11. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her *(past and current)* alcohol intake:

Yes (1) No (2)

Elig

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:

Yes (1) No (2)

Elig

D. Laboratory test exclusions

13. Hepatic Decompensation

a. Is the patient's serum albumin less than 3.2 g/dL:

Yes (1) No (2) → Elig

b. Is the patient's INR greater than 1.4:

Yes (1) No (2) → Elig

c. Is the patient's direct bilirubin greater than 1.0 mg/dL:

Yes (1) No (2) → Elig

d. Is the patient's total bilirubin greater than 3 mg/dL:

Yes (1) No (2) → Elig

e. Is the patient's hemoglobin less than 10 g/dL:

Yes (1) No (2) → Elig

f. Is the patient's white blood cell count less than 3,500 cells/mm^3:

Yes (1) No (2) → Elig

g. Is the patient's platelet count less than 130,000 cells/mm^3:

Yes (1) No (2) → Elig

h. Is the patient's neutrophil count less than 1,500 cells/mm^3:

Yes (1) No (2) → Elig

i. Does the patient have a history of esophageal varices, ascites, or hepatic encephalopathy:

Yes (1) No (2) → Elig

j. Tests are outside time window and clinic chose not to repeat tests:

Yes (1) No (2) → Elig

E. Medication use exclusions

14. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the past 12 months:

Yes (1) No (2) → Elig

15. Use of other known hepatotoxins within 90 days of liver biopsy or within 120 days of randomization:

Yes (1) No (2) → Elig

16. Initiation of any new medication/vitamin or supplement to treat NAFLD/NASH in the time period following liver biopsy and prior to randomization:

Yes (1) No (2) → Elig

F. Other chronic liver disease exclusions

17. Does the patient have ongoing autoimmune liver disease defined by liver histology:

Yes (1) No (2) → Elig

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:

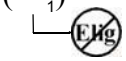
Yes (1) No (2) → Elig

19. Does the patient have alpha-1-antitrypsin (A1AT) genotype ZZ or SZ:

Yes (1) No (2) → Elig

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):

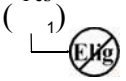
Yes (1) No (2)



21. Do any of the patient's assessments show evidence of other chronic liver disease

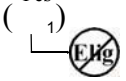
a. Suspected or proven liver cancer:

Yes (1) No (2)



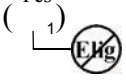
b. Hepatitis B (HBsAg):

Yes (1) No (2)



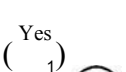
c. Hepatitis C (HCV RNA or anti-HCV):

Yes (1) No (2)



d. Any other type of liver disease other than NASH that warrants exclusion from the trial:

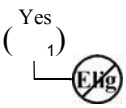
Yes (1) No (2)



G. Liver biopsy exclusions

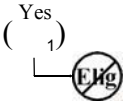
22. Inability to safely undergo a liver biopsy:

Yes (1) No (2)



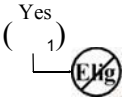
23. Biopsy out of window and patient chose not to repeat:

Yes (1) No (2)



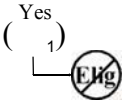
24. Biopsy inadequate for scoring and patient chose not to repeat:

Yes (1) No (2)



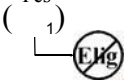
25. Local pathologist did not find NAFLD:

Yes (1) No (2)



26. NAFLD activity score (NAS) less than 4:

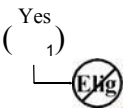
Yes (1) No (2)



H. Other medical exclusions

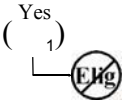
27. History of bariatric surgery or plans to have bariatric surgery during the CyNCh trial:

Yes (1) No (2)



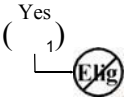
28. Inflammatory bowel disease (if active) or prior resection of small intestine:

Yes (1) No (2)



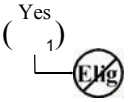
29. Active coagulopathy:

Yes (1) No (2)



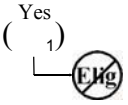
30. Active seizure disorders:

Yes (1) No (2)



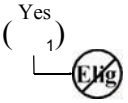
31. Gastrointestinal ulcers or other GI bleeding:

Yes (1) No (2)



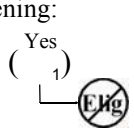
32. Renal dysfunction with a creatinine clearance of less than 90 mL/min/m^2:

Yes (1) No (2)



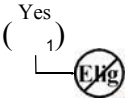
33. History of total parenteral nutrition (TPN) use in year prior to screening:

Yes (1) No (2)



34. History of heart disease (myocardial infraction, heart failure, unstable arrhythmias):

Yes (1) No (2)



35. Does the patient have clinically significant depression (patient was hospitalized for suicidal ideations or suicide attempts within the past 12 months):

Yes (1) No (2)
→ Elig

36. History of active malignant disease requiring chemotherapy or radiation in the past 12 months prior to randomization:

Yes (1) No (2)
→ Elig

37. Currently enrolled in a clinical trial or received an investigational study drug in the past 180 days:

Yes (1) No (2)
→ Elig

38. Other conditions which, in the opinion of the investigator, would impede compliance or hinder completion of the study:

Yes (1) No (2)
→ Elig

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):*

Yes (1) No (2)
→ Elig

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):*

Yes (1) No (2)
→ Elig

K. Eligibility check on day of randomization

41. Was an ineligibility condition checked or an eligibility not ascertained in items 9-40:

Yes (1) No (*2)
→ **50.**

**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:

Yes (1) → **50.**

No (2)

Task not run because patient is known to be ineligible (3) → **50.**

43. Based on today's physical examination, does the patient feel well today:

Yes (1) No (*2)
→ STOP

**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:

Yes (1) No (2)
→ **48.**

45. Is the patient of childbearing potential:

Yes (*1) No (2)
→ **48.**

**Administer pregnancy test.*

46. Is the patient pregnant *(positive pregnancy test on the day of randomization):*

Yes (*1) No (2)
→ Elig

**Go to item 50.*

47. Is the patient currently breast feeding

Yes (*1) No (2)
Elig

**Go to item 50.*

48. In the Study Physician's judgment, is there any reason to exclude the patient from randomization:

Yes (*1) No (2)
Elig

**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):*

Yes (*1) No (†2)
51. Elig

**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 9-49: (* 1)

b. Other reason not covered on this form *(specify):* (* 1)

_____
specify

**Go to item 53*

M. Physical Examination *(must be done on the day of randomization)*

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:

___ ___ ___ • ___
kgs

c. Weight group:

Less than or equal to 65kg (1)
Greater than 65 - 80kg (2)
Greater than 80kg (3)

N. Administrative information

53. Study Physician PIN:

___ ___ ___

54. Study Physician signature:

_____

55. Clinical Coordinator PIN: ___ ___ ___

56. Clinical Coordinator 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, patient 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 1

7. Study: CyNCh 8

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:

Yes (1) No (* 2)

STOP

** 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 (3)

C. Requirements for screening biopsy

10. Is this visit s:

Yes (1) No (2)

12.

11. Is the date in item 9a within 120 days of the anticipated date of randomization:

Yes (1) No (* 2)

Elig

** 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:

(Yes * 1) (No 2)

** If Yes, complete the Liver Tissue Banking (LT) form*

13. What stained slides from the biopsy are available at the clinical center *(check all that apply)*

a. H & E stain: (1)

b. Masson's trichrome stain: (1)

c. Iron stain: (1)

E. Unstained slides to be sent to the DCC

14. Are unstained slides available for sending to the DCC:

(Yes 1) (No 2)

17.

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)

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 3 unstained slides will be sent to the DCC)

17. Are any stained slides to be sent to the DCC:

(Yes 1) (No 2)

25.

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)

b. Slide sequence number of Masson's trichrome stain: ___ ___ (81-90)

c. Slide sequence number of iron stain: ___ ___ (81-90)

d. Slide sequence number of other stain: ___ ___ (81-90)

20. Are any stained slides to be returned to the clinic:

(Yes 1) (No 2)

25.

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)

b. Slide sequence number: ___ ___ (81-90)

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 (1)

At the end of the NASH CRN funding period (2)

24. Which pathology department did these slides come from:

NASH CRN clinical center's pathology department (1)

25. ___

Other, *(specify):* (2)

_____
name

_____
address

_____
address

_____
address

_____
phone

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.

G. Administrative information

25. Clinical Coordinator PIN: ____ ____ ____

26. Clinical Coordinator signature:

_____

27. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

CyNCh

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report: ____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: ____ ____ ____
If report not associated with a visit, fill in ''n.''

6. Form & revision: s r 1

7. Study: CyNCh 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:

Definitely yes (1)
Probably yes (2)
Possibly yes (3)
Probably no (4)
15.
Definitely no (5)
15.

12. Is this adverse event **serious**:

Yes (1) No (2)
15.

If Yes, then select all the reasons that apply:

a. Severity Grade 3, 4 or 5: (1)

b. Required inpatient hospitalization or prolonged existing hospitalization: (1)

c. Persistent or significant incapacity or disruption of ability to conduct normal life functions: (1)

d. Jeopardized patient and required medical or surgical intervention: (1)

e. Congenital anomaly or birth defect: (1)

13. Is this adverse event **unexpected**:

Yes (1) No (2)
15.

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:

Yes (*1) No (†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 (1)
Followup report (2)

17. Date of serious adverse event onset:

____ ____–____ ____ ____–____ ____
day mon year

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

____ ____–____ ____ ____–____ ____
day mon year

19. Describe the serious adverse event:

_____

_____

_____

_____

_____

20. Medications or supplements other than CyNCh study drug in use at the time of serious adverse event:

21. Specify tests/treatments and comorbidities:

22. Was an unscheduled liver biopsy performed:

(Yes *1) (No 2)

**Attach a copy of the institutional pathology report to the SR form.*

23. Did the serious adverse event result in significant sequelae:

(Yes 1) (No 2)

24.

Specify:

24. Short name for serious adverse event *(short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Studies and then click on CyNCh):*

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 CyNCh):*

Grade 3 - Severe	(1)
Grade 4 - Life threatening or disabling	(2)
Grade 5 - Death	(*3)

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

26. Did the serious adverse 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 *(complete and key CyNCh DR form):*	(1)
f. Other significant hazard or harm:	(1)
g. None of the above	(1)

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

Resolved	(1)
Active	(2) **29.**
Unknown	(3) **29.**

28. Date resolved:

____ ____–____ ____ ____–____ ____
day mon year

29. Additional comments on serious adverse event:

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 within 2 business days:

(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).

CyNCh

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

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of notification of intent to transfer:

____ ____–____ ____ ____–____ ____
day mon year

5. Visit code: n ____ ____

6. Form & revision: t n 1

7. Study: CyNCh 8

B. Last follow-up visit information

8. Date of last follow-up visit:

____ ____–____ ____ ____–____ ____
day mon year

9. Visit ID code of last completed follow-up visit: f ____ ____

10. Have cryovial and slide labels been sent to the adopting center:

Yes (1) No (*2)

** Send the cryovial and slide labels to the adopting center (using a package tracking service).*

C. Enrolling center administrative information

11. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

12. Clinical coordinator ID: ____ ____ ____

13. Clinical coordinator signature:

_____

D. Adopting center, patient and visit identification

14. Adopting center ID: ____ ____ ____ ____

15. Patient ID *(must be same as in Section A):*

____ ____ ____ ____

16. Patient code: *(must be same as in Section A):*

____ ____ ____

17. Expected date of first follow-up visit at adopting center:

____ ____–____ ____ ____–____ ____
day mon year

18. Visit ID code for expected first follow-up visit at adopting center: f ____ ____

Reminder: Please follow your local IRB requirements regarding consent and HIPAA statements.

E. Adopting center administrative information

19. Date form reviewed:

____ ____–____ ____ ____–____ ____
day mon year

20. Clinical coordinator ID: ____ ____ ____

21. Clinical coordinator signature:

_____

Fax form to the DCC. The DCC will key the TN form.