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) (No 2)

C

**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) (No 2)

Elig

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: (1) Elig

d. Hepatitis C: (1) Elig

e. Autoimmune hepatitis: (1) Elig

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

g. Wilson's disease: (1) Elig

h. Alpha-1-antitrypsin (A1AT) deficiency: (1) Elig

i. Hemochromatosis or iron overload: (1) Elig

j. Drug induced liver disease: (1) Elig

k. Ascites: (1) C

l. Gilbert's syndrome: (1)

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

n. Bleeding from varices: (1) Elig

o. Gastrointestinal ulcers or other gastrointestinal bleeding: (1) Elig

p. Biliary diversion: (1) C

q. Metabolic acidosis: (1) C

r. Edema: (1) C

s. Hepatic encephalopathy: (1) Elig

t. Any other evidence of chronic liver disease: (1) C

u. Currently active inflammatory bowel disease: (1) Elig

v. Short bowel syndrome: (1) C

w. Small intestine resection: (1) Elig

x. Renal dysfunction with creatinine clearance < 90 mL/min/m^2: (1) Elig

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

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) → 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 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) → C No (2)

**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) → C No (2)

**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:

(1) Yes (2) No

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:

(1) Yes (2) No

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:

(1) Yes (2) No

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:

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

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:

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

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:

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

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

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. 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: _____

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 the liver biopsy if the patient is nondiabetic or within **90 days of randomization if the patient is diabetic**. For the follow-up visit, date must be in the patient's time window (check patient's CyNCh visit time window guide).*

29. HbA1c *(if HbA1c is > 9.0%; 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

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

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

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 1

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)

(1) → Elig

C. Alcohol use exclusions

10. Does the patient have a history of significant alcohol intake:

Yes (1) No (2)

(1) → 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)

(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)

(2) → Elig

D. Laboratory test exclusions

13. Hepatic Decompensation

a. Is the patient's serum albumin less than 3.2 g/dL:

( ) Yes (1) → Elig ( ) No (2)

b. Is the patient's INR greater than 1.4:

( ) Yes (1) → Elig ( ) No (2)

c. Is the patient's direct bilirubin greater than 1.0 mg/dL:

( ) Yes (1) → Elig ( ) No (2)

d. Is the patient's total bilirubin greater than 3 mg/dL:

( ) Yes (1) → Elig ( ) No (2)

e. Is the patient's hemoglobin less than 10 g/dL:

( ) Yes (1) → Elig ( ) No (2)

f. Is the patient's white blood cell count less than 3,500 cells/mm^3:

( ) Yes (1) → Elig ( ) No (2)

g. Is the patient's platelet count less than 130,000 cells/mm^3:

( ) Yes (1) → Elig ( ) No (2)

h. Is the patient's neutrophil count less than 1,500 cells/mm^3:

( ) Yes (1) → Elig ( ) No (2)

i. Does the patient have a history of esophageal varices, ascites, or hepatic encephalopathy:

( ) Yes (1) → Elig ( ) No (2)

j. Tests are outside time window and clinic chose not to repeat tests:

( ) Yes (1) → Elig ( ) No (2)

E. Medication use exclusions

14. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the past 12 months:

( ) Yes (1) → Elig ( ) No (2)

15. Use of other known hepatotoxins within 90 days of liver biopsy or within 120 days of randomization:

( ) Yes (1) → Elig ( ) No (2)

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) → Elig ( ) No (2)

F. Other chronic liver disease exclusions

17. Does the patient have ongoing autoimmune liver disease defined by liver histology:

( ) Yes (1) → Elig ( ) No (2)

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) → Elig ( ) No (2)

19. Does the patient have alpha-1-antitrypsin (A1AT) genotype ZZ or SZ:

( ) Yes (1) → Elig ( ) No (2)

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) → Elig; 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) → Elig; No (2)

b. Hepatitis B (HBsAg):

Yes (1) → Elig; No (2)

c. Hepatitis C (HCV RNA or anti-HCV):

Yes (1) → Elig; No (2)

d. Any other type of liver disease other than NASH that warrants exclusion from the trial:

Yes (1) → Elig; No (2)

G. Liver biopsy exclusions

22. Inability to safely undergo a liver biopsy:

Yes (1) → Elig; No (2)

23. Biopsy out of window and patient chose not to repeat:

Yes (1) → Elig; No (2)

24. Biopsy inadequate for scoring and patient chose not to repeat:

Yes (1) → Elig; No (2)

25. Local pathologist did not find NAFLD:

Yes (1) → Elig; No (2)

26. NAFLD activity score (NAS) less than 4:

Yes (1) → Elig; No (2)

H. Other medical exclusions

27. History of bariatric surgery or plans to have bariatric surgery during the CyNCh trial:

Yes (1) → Elig; No (2)

28. Inflammatory bowel disease (if active) or prior resection of small intestine:

Yes (1) → Elig; No (2)

29. Active coagulopathy:

Yes (1) → Elig; No (2)

30. Active seizure disorders:

Yes (1) → Elig; No (2)

31. Gastrointestinal ulcers or other GI bleeding:

Yes (1) → Elig; No (2)

32. Renal dysfunction with a creatinine clearance of less than 90 mL/min/m^2:

Yes (1) → Elig; No (2)

33. History of total parenteral nutrition (TPN) use in year prior to screening:

Yes (1) → Elig; No (2)

34. History of heart disease (myocardial infraction, heart failure, unstable arrhythmias):

Yes (1) → Elig; 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) → Elig No (2)

36. History of active malignant disease requiring chemotherapy or radiation in the past 12 months prior to randomization:

Yes (1) → Elig No (2)

37. Currently enrolled in a clinical trial or received an investigational study drug in the past 180 days:

Yes (1) → Elig No (2)

38. 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

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. Physical Examination *(must be done on the day of randomization)*

41. Height *(shoes off)*

a. 1st measurement: ___ ___ ___ • ___

b. 2nd measurement: ___ ___ ___ • ___

c. Units:

Inches (1)
Centimeters (2)

42. 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)

43. Based on today's physical examination, does the patient feel well today:

Yes (1) No (*2) → Elig

**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.*

L. Eligibility check on day of randomization

44. Was an ineligibility condition checked or an eligibility not ascertained in items 9-40:

Yes (1) No (*2)

52.

**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.*

45. Were any stops or ineligible conditions other than "missing form RZ" identified by the Randomization Task:

Yes (1) → **52.**

No (2)

Task not run because patient is known to be ineligible (3) → **52.**

46. Is the patient male:

Yes (1) → **50.**

No (2)

47. Is the patient of childbearing potential:

Yes (*1) → **50.**

No (2)

**Administer pregnancy test.*

48. Is the patient pregnant *(positive pregnancy test on the day of randomization):*

Yes (*1) → Elig

No (2)

**Go to item 52.*

49. Is the patient currently breast feeding

Yes (*1) → Elig

No (2)

**Go to item 52.*

50. In 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 52:*

_____
specify reason

51. Does the patient still consent to randomization *(you should ask the patient to orally affirm his/her consent):*

Yes (*1) → **53.**

No (†2) → Elig

**Go to item 53 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.*

†Complete items 52-57 and key the form. The form must be keyed to document the reasons for ineligibility for CyNCh.

M. Reasons for ineligibility for ineligible patients

Note: Complete this section for ineligible patients only.

52. Reason for ineligibility *(check all that apply)*

a. Reason covered in items 9-51: (1)

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

_____
specify

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

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) → Elig ( ) No (2)

b. Is the patient's INR greater than 1.4:

( ) Yes (1) → Elig ( ) No (2)

c. Is the patient's direct bilirubin greater than 1.0 mg/dL:

( ) Yes (1) → Elig ( ) No (2)

d. Is the patient's total bilirubin greater than 3 mg/dL:

( ) Yes (1) → Elig ( ) No (2)

e. Is the patient's hemoglobin less than 10 g/dL:

( ) Yes (1) → Elig ( ) No (2)

f. Is the patient's white blood cell count less than 3,500 cells/mm^3:

( ) Yes (1) → Elig ( ) No (2)

g. Is the patient's platelet count less than 130,000 cells/mm^3:

( ) Yes (1) → Elig ( ) No (2)

h. Is the patient's neutrophil count less than 1,500 cells/mm^3:

( ) Yes (1) → Elig ( ) No (2)

i. Does the patient have a history of esophageal varices, ascites, or hepatic encephalopathy:

( ) Yes (1) → Elig ( ) No (2)

j. Tests are outside time window and clinic chose not to repeat tests:

( ) Yes (1) → Elig ( ) No (2)

E. Medication use exclusions

14. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the past 12 months:

( ) Yes (1) → Elig ( ) No (2)

15. Use of other known hepatotoxins within 90 days of liver biopsy or within 120 days of randomization:

( ) Yes (1) → Elig ( ) No (2)

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) → Elig ( ) No (2)

F. Other chronic liver disease exclusions

17. Does the patient have ongoing autoimmune liver disease defined by liver histology:

( ) Yes (1) → Elig ( ) No (2)

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) → Elig ( ) No (2)

19. Does the patient have alpha-1-antitrypsin (A1AT) genotype ZZ or SZ:

( ) Yes (1) → Elig ( ) No (2)

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 → Elig

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 → Elig

b. Hepatitis B (HBsAg):

( ) Yes 1 ( ) No 2 → Elig

c. Hepatitis C (HCV RNA or anti-HCV):

( ) 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

G. Liver biopsy exclusions

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 NAFLD:

( ) Yes 1 ( ) No 2 → Elig

26. NAFLD activity score (NAS) less than 4:

( ) Yes 1 ( ) No 2 → Elig

H. Other medical exclusions

27. History of bariatric surgery or plans to have bariatric surgery during the CyNCh trial:

( ) Yes 1 ( ) No 2 → Elig

28. Inflammatory bowel disease (if active) or prior resection of small intestine:

( ) Yes 1 ( ) No 2 → Elig

29. Active coagulopathy:

( ) Yes 1 ( ) No 2 → Elig

30. Active seizure disorders:

( ) Yes 1 ( ) No 2 → Elig

31. Gastrointestinal ulcers or other GI bleeding:

( ) Yes 1 ( ) No 2 → Elig

32. Renal dysfunction with a creatinine clearance of less than 90 mL/min/m^2:

( ) Yes 1 ( ) No 2 → Elig

33. History of total parenteral nutrition (TPN) use in year prior to screening:

( ) Yes 1 ( ) No 2 → Elig

34. History of heart disease (myocardial infraction, heart failure, unstable arrhythmias):

( ) Yes 1 ( ) No 2 → Elig

35. Does the patient have clinically significant depression (patient was hospitalized for suicidal ideations or suicide attempts within the past 12 months):

( ) Yes (1) → Elig
( ) No (2)

36. History of active malignant disease requiring chemotherapy or radiation in the past 12 months prior to randomization:

( ) Yes (1) → Elig
( ) No (2)

37. Currently enrolled in a clinical trial or received an investigational study drug in the past 180 days:

( ) Yes (1) → Elig
( ) No (2)

38. 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

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) → **50.**
( ) No (*2)

**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) → **48.**
( ) No (2)

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) → Elig
( ) No (2)

**Go to item 50.*

47. Is the patient currently breast feeding

Yes (*1) No (2)
(*1) → 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)
(*1) → 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. ← (*1) Elig ← (†2)

**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