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 v	visit identification	5. Visit code: if report not associated v	vith a visit. fill in "n"
1. Center ID:		J	, , ,
		6. Form & revision:	<u>a</u> <u>e</u> <u>1</u>
2. Patient ID:			C NCL 0
		7. Study:	CyNCh 8
3. Patient code:			
4. Date of report:			
day	mon year		

B. Visit interval identification

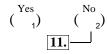
8. Since the last visit, has the patient had a reportable event:

Y	es	(No \
(1)	(2)
		33.	ل

9. Most recently completed visit prior to adverse event

a. Date:		
day	mon	year

- **b.** Visit code:
- 10. Since the last visit, has the patient had any ER visits or hospitalizations:



If Yes, specify reason and list dates:

If none for items 10a or 10b, enter "00".

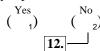
a. Number of hospitalizations:

hospitalizations

b. Number of Emergency Room visits:

 # visits	

11. Since the last visit, has the patient had any health problems not already reported:



If Yes, specify health problem and list dates:

1 cs, s _F	seegy ne	cui i pro	ovem une	i tist cicii	cs.

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)
----	------	------------	--------	---	----

*CyNCh study drug will be discontinued if a patient becomes pregnant. Contact the NASH CRN

Data Coordinating Center to unmask the study drug.

17. Describe event:			20. Severity grade:
			Not an adverse event (₀)
			Grade 1 - Mild
			Grade 2 - Moderate
			Grade 3 - Severe (3)
			Grade 4 - Life threatening or disabling (4)
			Grade 5 - Death (* ₅)
			*Complete and key Death Report (DR) form.
For items 18, 19, and 20, please refer to			21. Randomization in CyNCh
v3.0 available at www.nashcrn.com; click and then CyNCh.	on Studio	es	a. Has patient been randomized in CyNCh:
18. Identify body system (check all that	apply)		$\begin{pmatrix} \text{Yes} & \text{No} \\ 1 \end{pmatrix} & \begin{pmatrix} \text{No} \\ 2 \end{pmatrix}$
a. Auditory/ear:	(1)	29.
b. Allergy/immunologic:	(1)	b. Date randomized in CyNCh:
c. Ocular/visual:	(1)	
d. Hepatobiliary/pancreatic:	(1)	day mon year
e. Infection:	(1)	22. Is the patient currently receiving the
f. Constitutional symptoms:	(1)	CyNCh study drug: ${{\rm Yes}\choose{1}} \qquad {{\rm No}\choose{2}}$
g. Psychiatric:	(1)	$\begin{pmatrix} 1 \end{pmatrix} \begin{pmatrix} 2 \end{pmatrix}$
h. Cardiovascular:	(1)	23. Patient's history of treatment with
i. Dermatologic/skin:	(1)	CyNCh study drug
j. Endocrine/metabolic:	(1)	 a. How long has patient been on study drug:
k. Gastrointestinal/digestive:	(1)	uiug.
l. Lymphatic/blood:	(1)	b. What daily dose was the patient
m. Musculoskeletal:	(1)	taking prior to the adverse event:
n. Neurologic:	(1)	
o. Pulmonary/respiratory:	(1)	mg/day
p. Renal/genitourinary:	(1)	c. Have there been any treatment interruptions or restarts:
q. Sexual/reproductive:	(1)	Yes No
r. Other (specify):	(1)	Include stop/restart dates and reasons: $\binom{1}{2}$
specify other body system			
s. None of the above:	(1)	
19. Short name for event if applicable:			
Not applicable	(0	

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

Definitely yes	(1/
Probably yes	(2
Possibly yes	(3,
Probably no	(4
Definitely no	(_`

25. Is this a serious adverse event:

Yes	No
$\begin{pmatrix} 1 \end{pmatrix}$	(2
	26.

1)

1)

If Yes, then select all the reasons that \overline{apply} :

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



27. Reason the adverse event was unexpected:

Not listed in the cysteamine bitartrate investigator's brochure

(.

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

(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

- (,)
- **28.** Did you select "Yes" for items 24 (definitely, probably, or possibly), 25, and 26:

Yes	No
$(*_{1})$	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
~ .	

*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
Unknown	<u>31.</u> (₃
	31.

30. Date adverse event resolved:

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

31. What action was taken:

-		

32. Other comments on event:

Patient ID:	 	

10	A 1		4.		4.
М.,	Aar	ninisii	ranve	inior	mation

33.	Clinical	Coordinator	PIN:			
34.	Clinical	Coordinato	signature:			
35.	Study Ph	ysician PIN	ī:			
36.	Study Pł	ıysician sigr	nature:			
37.	Date for	n reviewed:		_	_	
		day	mon		ye	ear

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 c is checked for an item, the patient is ineligible and cannot enroll in CyNCh. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

Α.	Center,	visit.	and	patient	identi	fication
7 A.	Control ,	1 1010	ullu	patient	Iuciiu	11cution

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

day	mon	year

5. Visit code:

- _S_____
- **6.** Form & revision:
- <u>b</u> <u>h</u> _1_

7. Study:

B. NAFLD history

8. Does the patient have a liver biopsy done that you want evaluated for the CyNCh trial (complete the Liver Biopsy Histology Findings (HF) and Liver Biopsy Materials Documentation (SD) forms for this biopsy):

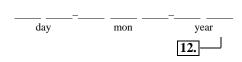


*Randomization must be done within 120 days of liver biopsy.

9. Date of liver biopsy:



10. Last day to randomize based on liver biopsy date (120 days after biopsy; use date calculator 2 on the NASH CRN home page):



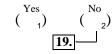
11. Will the patient have a biopsy during screening:



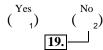
*Blood draw for banking should be done **prior** to the biopsy or at least 4 days **after** the biopsy.

C. Menstrual history and use of effective birth control

12. Is the patient female:



- 13. Menarche history
 - a. Has menarche occurred:



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

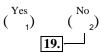
age	in	years

14. Characterize the menstrual history in the past year (*check only one*):

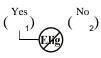
Regular periods (
Irregular periods (
Rare periods (

No periods (

15. Is the patient of childbearing potential:



16. Is the patient currently pregnant:

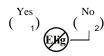


17. Is the patient currently breastfeeding:



*Caution: Patient cannot be breastfeeding at time of randomization.

18. If sexually active, is the patient willing to use two effective birth control methods during CyNCh:



- **D. Medical history** (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:



d. Hepatitis C:



e. Autoimmune hepatitis:



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



g. Wilson's disease:



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



i. Hemochromatosis or iron overload:



j. Drug induced liver disease:



k. Ascites:



l. Gilbert's syndrome:



m. Esophageal or gastric varices on endoscopy:



n. Bleeding from varices:



o. Gastrointestinal ulcers or other gastrointestinal bleeding:



p. Biliary diversion:



q. Metabolic acidosis:



r. Edema:



s. Hepatic encephalopathy:



t. Any other evidence of chronic liver disease:



u. Currently active inflammatory bowel disease:



v. Short bowel syndrome:



w. Small intestine resection:



x. Renal dysfunction with creatinine clearance < 90 mL/min/m²:



y. Hemophilia (bleeding disorder):



z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (

aa. Endocrine disease (hormonal abnormality):	(,)	ax. Dermatologic disorders:	(1)
•	()	ay. Myopathy:	(1)
ab. Asthma:	(1)	az. Myositis:	(1)
ac. Hepatocellular carcinoma:		ba. Major depression:	(1)
ad. Other malignancy (cancer):		bb. Schizophrenia:	(1)
as Astive melionent disease magninim	<u> </u>	bc. Bipolar disorder:	(1)
ae. Active malignant disease requiring chemotherapy or radiation within	•	bd. Obsessive compulsive disorder:	(1)
past year:	(₁)	be. Severe anxiety or personality disorder:	(1)
af. Human immunodeficiency virus (HIV):	(1)	bf. Substance abuse:	(
ag. Peripheral neuropathy:	(')	bg. None of the above:	(1)
ah. Active seizure disorder or epileps	sy: (₁)	20. Has the patient ever had bariatric su for any of the following (check all to	
ai. Drug allergies:	(₁)	a. Stapling or banding of the stomac	ch: ()
aj. Hypothyroidism:	(1)	b. Jejunoileal (or other intestinal)	
ak. Hypertension:	(1)	bypass:	\bigcirc $($ $_{1})$
al. Cerebrovascular disease:	(1)		(Elig)—
am. Hyperlipidemia (high cholestero high triglycerides):	l, (₁)	c. Biliopancreatic diversion:	
an. Pancreatitis:	(1)	d. Other bariatric surgery (<i>specify</i>):	(,)
ao. Cholelithiasis:	(1)	g J (2p 4,5)	$\langle \mathbf{C} \rangle$
ap. Coronary artery disease:			
aq. Congestive heart failure:	(1)	e. None of the above:	(1)
ar. Myocardial infarction:	· (')	21. Is the patient currently undergoing evaluation for bariatric surgery:	N.
·	C -	(L	$\binom{NO}{1}$ $\binom{NO}{2}$
as. Unstable arrhythmias:	\bigcirc	20 W d d d d d d d d d d	
at. Elevated uric acid such as gout:	(₁)	22. Has the patient received total parent nutrition (TPN) in the past year:	eral
au. Kidney disease:	<u>(</u> 1)	(L) (NO 2)
av. Polycystic ovary syndrome:	$\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$		
aw. Sleep apnea:	(1)		

- 23. Organ, limb, or bone marrow transplant
 - **a.** Has the patient ever received a liver transplant:



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

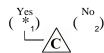
Yes		No		
(1)	(2)	

E. Drugs historically associated with NAFLD

- **24.** Has the patient used any tetracyclines, salicylates, valproic acid or other known hepatotoxins in the past year (check all that apply)
 - **a.** Amiodarone (Pacerone):
 - **b.** Demeclocycline (Declomycin): (1)
 - **c.** Divalproex (Depakote): (1)
 - **d.** Doxycycline (Monodox):
 - **e.** Isonicotinylhydrazine (INH, Isoniazid, Tubizid): (,)
 - **f.** Isotretinoin (Accutane, Amnesteem, Clarvis, or Sotret):
 - **g.** Methotrexate (Rheumatrex):
 - **h.** Minocycline (Dynacin, Minocin):
 - i. Oxytetracycline (Terramycin):
 - **j.** Tetracycline (Achromycin): (₁)
 - **k.** Valproate sodium (Depacon):
 - **l.** Valproic acid (Depakene): (1)
 - **m.** Other known hepatotoxin (specify): (

n. None of the above:	(1)

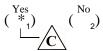
25. Were any of the items in 24a-m checked:



*Caution: Use of any of these drugs for more than 2 consecutive weeks in the past year or in the 90 days prior to liver biopsy is exclusionary.

26. Has the patient taken any systemic glucocorticoids in the past year (*check all that apply*)

- **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: (,)
- i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (,)
- **j.** Other, (specify):
- **k.** Other, (specify):
- **l.** None of the above:
- **27.** Were any of the items 26a-k checked:

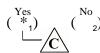


*Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past year is exclusionary.

28.	Has the patient taken any anabolic
	steroids or tamoxifen in the past year
	(check all that apply)

a.	Boldenone	undecylenate	(Equipoise):	(1)
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29. Were any of the items 28a-1 checked:



*Caution: Use of anabolic steroids or tamoxifen for more than 2 consecutive weeks in the past year is exclusionary.

30. Does the patient have a known intolerance to cysteamine bitartrate:

Yes	No
	(2)

F. Use of antidiabetic drugs

31. Has the patient used any antidiabetic medications in the past 6 months:

	1	. es	110	
	(1)	(2	(
		3	32.	
check all that apply)				

a.	Acarbose (Precose):	(1)	
b.	Acetohexamide (Dymelor):	(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:

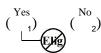
Yes	(No
	34.

(If yes, check all that apply)

- **a.** Betaine (Cystadone):
- **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler):
- **c.** Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
- **d.** S-Adenylmethionine (SAM-e):
- e. Milk thistle:
- **f.** Probiotics: (,)
- **g.** Gemfibrozil (Gen-Fibro, Lopid): (1)
- **h.** Vitamin E: (1)
- **i.** Other (specify):

specify

33. Were any of the medications/supplements checked in items 32a-i initiated after the screening liver biopsy being used for CyNCh:



34. Has the patient taken any vitamins in the past 6 months:

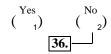


(If yes, check all that apply)

- a. Vitamin A:
- **b.** Vitamin B (any type):
- **c.** Vitamin C:
- **d.** Vitamin D: (1)
- e. Vitamin E: (
- **f.** Multivitamin:
- **g.** Other, (specify):

H. Use of statins, fibrates, and antiobesity drugs

35. Has the patient taken any lipid lowering medications in the past 6 months:



(If yes, check all that apply)

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

36. Has the patient taken any antiobesity medications in the past 6 months:

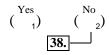


(If yes, check all that apply)

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

I. Use of other medications and supplements

37. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 6 months:



(If yes, check all that apply)

- **a.** Acetaminophen (Tylenol): (1)
- **b.** Aspirin 325 mg: (₁)
- **c.** Ibuprofen (Advil, Motrin):
- **d.** Naproxen (Aleve, Naprosyn): (1)
- **e.** Other, (specify):
- **f.** Other, (specify):

38. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 6 months:

Y	es es	N	Vо
(1)	(2)
	3	. —	J

(If yes, check all that apply)

- **a.** Cimetidine (Tagamet):
- **b.** Esomeprazole magnesium (Nexium):
- c. Famotidine (Pepcid):
- **d.** Lansoprazole (Prevacid):
- e. Nizatidine (Axid):
- **f.** Omeprazole (Prilosec):
- **g.** Ranitidine (Zantac):
- **h.** Ranitidine bismuth citrate (Tritec):
- i. Antacids, (specify):
- **j.** Other, (specify):
- **k.** Other, (specify):

39. Has the patient taken any cardiovascular/antihypertensive medications in the past 6 months:

Yes		No		
(.	1)	(2)	
	4	0. —	J	

(If yes, check all that apply)

- **b.** Aspirin 81 mg: (1)
- c. Atenolol (Tenormin):
- **d.** Benazepril (Lotensin):
- **e.** Captopril (Capoten): (1)
- **f.** Clonidine (Catapres): (1)
- g. Digoxin (Lanoxin):
- **h.** Diltiazem (Cardizem):
- i. Doxazosin (Cardura):
- i. Doxazosiii (Cardura).
- j. Enalapril (Vasotec):
- **k.** Felodipine (Plendil): (

 1. Furosemide (Lasix): (

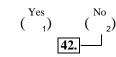
 1. Furosemide
- **m.** Hydrochlorothiazide (Esidrix, HydroDIURIL):
- **n.** Hydrochlorothiazide + triamterene (Dyazide): (1)
- o. Lisinopril (Prinivil, Zestril):
- **p.** Losartan potassium (Cozaar):
- **q.** Losartan potassium with hydrochlorothiazide (Hyzaar): (1)
- **r.** Metoprolol (Lopressor): (1)
- s. Nifedipine (Adalat, Procardia): (1)
- **t.** Perhexiline maleate: (1)
- **u.** Propranolol (Inderal): (1)
- v. Quinapril (Accupril):
- **w.** Terazosin (Hytrin): (1)
- **x.** Timolol maleate (Blocadren): $\binom{1}{1}$
- y. Valsartan (Diovan): (1
- **z.** Verapamil (Calan):
- aa. Other, (specify):
- **ab.** Other, (specify):

40. Has the patient taken any allergy or asthma medications in the past 6 months that have not already been reported on this form:

Y	es	No			
(1)	(2)		
	4	I 1. —	J		

(If yes, check all that apply)

- **a.** Albuterol:
- **b.** Beclomethasone dipropionate (Beclovent, Vanceril):
- **c.** Budesonide (Pulmicort, Rhinocort): (1)
- **d.** Fluticasone propionate (Flonase, Flovent):
- e. Loratadine (Claritin):
- **f.** Mometasone furoate (Nasonex):
- **g.** Triamcinolone acetonide (Azmacort, Nasacort):
- **h.** Other, (specify):
- i. Other, (specify):
- **41.** Has the patient taken any antipsychotic or antidepressant medications in the past 6 months:



(If yes, check all that apply)

- **a.** Aripipazole (Abilify):
- **b.** Buporpion (Wellbutrin): (1)
- **c.** Clomipramine (Anafranil): (1)
- d. Escitalopram (Lexapro): (1)e. Fluoxetine (Prozac): (1)
- **f.** Fluvoxamine (Luvox):
- **g.** Lithium (Eskalith, Lithobid): (1)
- **h.** Quetiapine (Seroquel):
- i. Risperidone (Risperdal):
- **j.** Sertraline (Zoloft): $\begin{pmatrix} 1 \end{pmatrix}$
- **k.** Other (specify):

42. Has the patient taken any supplements in the past 6 months that have not already been reported on this form:

Yes	No
$\begin{pmatrix} & & 1 \end{pmatrix}$	(2)
	43.

(If yes, check all that apply)

a. Alpha-lipoic acid:	(1)	

- **b.** Beta-carotene: (1)
- c. Calcium (any form):
- **d.** Carnitine (any form):
- e. Chondroitin (any form):
- **f.** Cod liver oil:
- **g.** Coenzyme Q:
- **h.** Dichloroacetate: $\begin{pmatrix} 1 \end{pmatrix}$
- i. Echinacea:
- **j.** Fish oil (any form): $\binom{1}{1}$
- **k.** Flax seed oil: (1)
- **l.** Garlic: (₁)
- **m.** Ginkgo biloba:
- **n.** Glucosamine (any form): $\binom{1}{1}$
- **o.** Lecithin: (1)
- **p.** Magnesium: (1)
- **q.** N-acetyl-cysteine: (1)
- **r.** Potassium (any form):
- s. Saw palmetto: (1)
- **t.** Selenium: (1)
- ${f u.}$ St. John's Wort:
- v. Taurine: (1)
- w. Zinc picolinate: (1)
- **x.** Other, (specify):

y. Other, (specify):	(1)

43. Has patient taken any of the following medications in the past 6 months:

Yes	No
(₁)	(2)
	44.

(If yes, check all that apply)

- **a.** Isotretinoin (Accutane): (1)
- **b.** Levonorgestrel (Norplant):
- c. Levothyroxine (Levoxyl, Synthroid): (
- **d.** Liothyronine (Cytomel): (1)
- e. Oral contraceptives:
- **f.** Penicillamine (Cuprimine, Depen): (1)
- **g.** Trientine hydrochloride (Syprine): (1)
- **h.** Other, (specify):
- i. Other, (specify):
- j. Other, (specify):
- **k.** Other, (specify):
- l. Other, (specify):
- J. Administrative information
- **44.** Study Physician PIN:
- **45.** Study Physician signature:
- **46.** Clinical Coordinator PIN:
- **47.** Clinical Coordinator signature:
- ____

48. Date form reviewed:

		-
day	mon	year

Central Histology Review

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

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

By whom: Data Coordinating Center staff.

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

	A. Clinic, patient and visit identification
	1. Center ID
	2. Patient ID
	3. Patient code
////	4. Date of central reading
	5. Visit code
<u>c r 2</u>	6. Form and revision
	7. Study: 6 =Database 2; 7 =FLINT; 8 =CyNCh
//	8. Date of biopsy
	B. Slide sequence number9. Sequence number for a. H & E stained slide
	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. His H & E stain	stology
13. Steatosis (assume macro, e.g., large and small drople	t)
a. Grade: 0 =<5%; 1 =5-33%; 2 =34-66%; 3 =>66%	
b. Location: 0 =Zone 3 (central); 1 =Zone 1 (periport	al); 2=Azonal; 3=Panacinar

2=Predominantly small droplet

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

... c. Type of macrovesicular steatosis: 0=Predominantly large droplet; 1=Mixed large and small droplet;

_ Patient ID	D. Histology (contra)
14. Inflammation	
	obular inflammation: combines mononuclear, fat granulomas, and pmn foci:
	under 20x mag; 2 =2-4 under 20 mag; 3 =>4 under 20 mag
	lomas seen: 0 =No; 1 =Yes
	ranulomas seen: 0 =No; 1 =Yes
_	portal, chronic inflammation: 0 =None; 1 =Mild; 2 =More than mild
u. Amount of j	portal, enrolle inflammation. 6 —1000c, 1—1010c than find
15. Liver cell injur	
	0 =None → GOTO Item 15d ; 1 =Few; 2 =Many
	poning present: 0=No; 1=Yes
	lloon cells present: 0=No; 1=Yes
_ , , , , , , , , , , , ,	odies: 0=Rare/absent; 1=Many
	nacrophages (Kupffer cells): 0=Rare/absent; 1=Many
	nondria: 0 =Rare/absent; 1 =Many
1. 1.105011110011	ionalia. V Italo accomi, 1 Ivially
16. Mallory-Denk	bodies: 0 =Rare/absent; 1 =Many
_ 10,1,1,1,1,1,1,1	0001001 0 1101101 00000111, 1 1110111
17. Glycogen nucl	ei: 0=Rare/absent; 1=Present in patches
18. Glycogenosis o	of hepatocytes: 0 =Not present; 1 =Focal, involving less than 50% of the hepatocytes; 2 =Diffuse,
	ter than or equal to 50% of the hepatocytes
	, , , , , , , , , , , , , , , , , , ,
19. Masson's tric	hrome stain
a. Fibrosis stag	ge: 0=None → GOTO Item 20; 1a=Mild, zone 3 perisinusoidal (requires trichrome);
	rate, zone 3, perisinusoidal (<i>does not require trichrome</i>); 1c =Portal/periportal only;
	and periportal, any combination; 3=Bridging; 4=Cirrhosis
	dal 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
	t location of fibrosis: 0=More predominance around or between portal areas; 1=No portal or
	edominance; 2=More predominance around/between central veins
20. Iron stain	
a. Hepatocellu	lar iron grade: 0 =Absent or barely discernible, $40x \rightarrow GOTO$ item $20c$;
1=Barely	discernable granules, 20x; 2 =Discrete granules resolved, 10x; 3 =Discrete granules resolved, 4x;
4=Masses	visible by naked eye
b. Hepatocellu	llar iron distribution: 0 =Periportal; 1 =Periportal and midzonal; 2 =Panacinar; 3 =Zone 3 or azonal
	ellular iron grade: 0=None → GOTO item 21; 1=Mild; 2=More than mild
	ellular 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
	patitis? 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 pre	sent? 0 =No → GOTO item 25 ; 1 =Yes
_ 23. Is this cryptoge	enic cirrhosis: 0=No → GOTO item 25; 1=Yes
	estive of steatohepatitis etiology for cryptogenic cirrhosis:
	nk bodies (rule out cholate stasis): 0 =Absent; 1 =Present
	dal fibrosis away from septa: 0 =Absent; 1 =Present
	ballooning: 0=Absent; 1=Present
	nondria: 0=Absent; 1=Present
e. Other notab	le findings: 0 =Absent; 1 =Present; Specify:
25 04	
25 Other commen	te [,]

LR - Laboratory Results - Tests Done at Screening and Followup Visits

Purpose: To record archival and current laboratory test results for tests done during both screening and followup.

When: Visits s, f04, f12, f24, f36, f52, and f76.

Administered by: Study Physician and Clinical Coordinator.

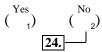
Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. Attach copies of the laboratory reports to this form. If we is checked for any item, then the form should not be keyed.

A. Center, patient, and visit ide	ntification	12. White blood cell values			
1. Center ID:		a. White blood cell count (WBC):			
2. Patient ID:		If WBC $< 3.5 \cdot 10^3$ cel tient is ineligible.	10^3 cells/ μ L or 10^9 cells/L lls/mm ³ at screening, pa-		
3. Patient code:					
4. Date of visit:		b. Neutrophils:If neutrophils < 1500 patient is ineligible.	cells/µL cells/mm ³ at screening,		
day n	oon year	c. Lymphocytes:	cells/ μL		
6. Form & revision:	<u>l r 1</u>	d. Monocytes:			
7. Study:	CyNCh 8	e. Eosinophils:	cells/ μL cells/ μL		
B. Hematology Required at all visits.		f. Basophils:	cells/ μL		
8. Date of blood draw for compount:	blete blood	13. Platelet count:			
day n Date must be within the re within 90 days of liver biopsy for the followup visit (check visit time window guide).	or in the time window	If platelets < 130,000 conscreening, patient is inel	cells/mm ³ $(mm^3 = \mu L)$ at igible.		
9. Hemoglobin: If hemoglobin < 10 g/dL at ineligible.	g/dL screening, patient is				
10. Hematocrit:					
11. Mean corpuscular volume (N	MCV):				

C. Chemistries

Required at visits s, f24, f52, and f76.

14. Is metabolic panel required at this visit:



	_	_			_	_	_	
15	Data	Ωť	hloo	d dra	w for	cha	miet	riac
1.	Date	w	1711/1/1	u ura	w ioi	CHC	шыы	LILO

	_		_
	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).

11	C 1'	
10.	Sodium	

mFa/I	

17	Pota	ssium
1/.	rota	SSIUIII

	•	
mF	a/L	

•	
mg/dL	

21.	Blood	urea nitrogen	(BUN))

~~	\sim	. •	•	
,,,	Crea	tir	าาท	ρ
	Cica	un	1111	·

•	
 mg/dL	_

73	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

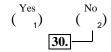
Date must be in the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).

•	
sec	

E. Hemoglobin A1c

Required at visits s, f24, f52, and f76.

27. Is HbA1c required at this visit:



28. Date of blood draw for HbA1c:

_		_		
day	mon		vear	

Date must be within the required time window: within 90 days of 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	vear

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	
	T.T./T	

a. Upper limit of normal:

	U/L	

Patient ID:	 	

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:



40. Was participant fasting for at least 8 hours prior to blood draw:



*12 hour fasting is preferred, but will accept nonfasting lipid values.

41. Date of blood draw for fasting lipid profile:

day	mon	year

Date must be within the required time window; within 90 days of liver biopsy or in the time window for the followup visit (check the patient's CyNCh visit time window guide).

a. Triglycerides:

mg/c	lL.

b. Total cholesterol:

mg/dL	

c. HDL cholesterol level:

n	ng/dL	

d. LDL cholesterol level*:

	mg/dL	
be	calculated due	te

*Enter "GT" if LDL cannot high triglycerides.

H. Fasting glucose and insulin

Required at visits s, f24, f52, and f76.

42. Are glucose and insulin required at this visit:



43. Was participant fasting for at least 8 hours prior to blood draw:



*Patient must be fasting; 12 hour fasting is preferred. Fasting glucose and insulin must be obtained at visit s.

44. Date of blood draw for fasting glucose and insulin:

=		_
day	mon	year

Date must be within 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/m	ıL	

I. Pregnancy test

Required at all study visits, if applicable.

45. Is pregnancy test applicable:



46. Date of urine collection (or blood draw):

day	m	non	year	
	-	-		

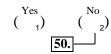
Date must be the same day as date of visit.

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:



49. Was the patient found to be ineligible based on hemoglobin (item 9), WBC (item 12a), neutrophils (item 12b), platelet count (item 13), albumin (item 36), INR (item 26), HbA1c (item 29), bilirubin total (item 31), direct bilirubin (item 32), pregnancy test (item 47), or based on missing tests:



K. Administrative information

50.	Study	Phy	ysicia	n PIN:				
-----	-------	-----	--------	--------	--	--	--	--

-	_	_
day	mon	year

MV - Missed or Incomplete Visit

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

When: At the close of a visit window for any missed follow-up visit or for any follow-up visit with specific forms not completed. Use visit code f04, f12, f24, f36, f52 or f76.

Respondent: None.

Completed by: Clinical Coordinator.

Instructions: Complete this form when a patient fails to complete a visit or specific visit procedures (resulting in missing forms) within the time window for the visit.

A. Center, patient, and visit identification			10. Steps taken to avoid missing the visit (<i>check all that apply</i>)		
1. Center ID:			a. Telephoned patient:	(1)
			b. Mailed reminder card:	(1)
2. Patient ID:			c. Other (specify):	(1)
3. Patient code:			specify		
4. Date form completed:			14.]—	J
day mon	year		D. Missed form information		
5. Visit code: <u>f</u>			11. Check form(s) not completed (check all that apply)		
6. Form & revision:mv_	1	<u>L</u>	a. Blood Processing for Plasma and Serum (BP):	(1)
7. Study: CyNC	h_8	8_	b. Follow-up Medical History (FH):	(1)
•			c. Symptoms of Liver Disease (LP):	(1)
B. Reason for completion of this form			d. Laboratory Results - Tests Done During Screening and Follow-up (LR):	(1)
8. Was the entire visit missed: (Yes (No 11.		[o	e. Liver Tissue Banking (LT):	(1)
		₂)	f. Nutrition Data Documentation for NDSR (ND):	(1)
C. Missed visit information			g. Physical Examination (PE):	(1)
C. Missed visit information			h. Focused Physical Examination (PF):	(1)
9. Reason for missed visit (check all that app	oly)		i. Parent Report for Teens (13-17) (PQ):	(1)
a. Patient was ill:b. Patient was temporarily away from	(1)	j. Pediatric QOL: Parent Report for Child (8-12) (PR):	(1)
area:	(1)	k. Pediatric QOL: Child Report (PW):	(1)
c. Patient refused to return:	(1)	l. Pediatric QOL: Teen Report (PY):	(1)
d. Patient has permanently moved from the area:	(1)	m. Study Drug Dispensing and Return (RD):	(1)
e. Unable to contact patient:	(1)	n. Liver Biopsy Materials Documentation (SD):	(₁)
f. Other (specify):	(1)	o. MRI Consent and Report Form (MR):	(1)
specify			p. Other (specify):	(1)
specify			specify		

- 12. Reason form(s) not completed
 (check all that apply)

 a. Patient was ill:

 b. Patient/parent refused procedure:

 c. Procedure forgotten:

 d. Other (specify):

 specify

 13. Attempts made to complete form(s)
 (check all that apply)
- a. Attempted to reschedule procedure:

 b. Attempted to collect interview data by phone from patient/parent:

 c. Attempted to gain patient/parent cooperation:

 d. Other (specify):

 (check all that apply)

 (a)

 (b)

 (c)

 (c)

 (c)

 (d)

 (d)

E. Administrative information

14. Clinical Coordinator PIN: ____ ___

specify

- **15.** Clinical Coordinator signature:

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 i	dentification	9. Weight (shoes off)		
1. Center ID:		a. Weight, 1st measurement:		
2. Patient ID:		b. Weight, 2nd measurement:		
3. Patient code:		c. Units:		
4. Visit date:		Pounds Kilograms	(1) 2)
day 5. Visit code:	mon year	10. Waist (standing, at midpoint between high of iliac crest and lowest part of costal repeat waist measurements until you homeasurements within 4 in (10.2 cm) of each	mar; ave	gin; two
6. Form & revision:	_pe1_	a. Circumference, 1st measurement:		
7. Study:	CyNCh 8	b. Circumference, 2nd measurement:	 ce	
B. Measurements		waist circumference		
8. Height (shoes off) a. 1st measurement:	•	c. Units: Inches Centimeters	(1) 2)
b. 2nd measurement:	•			
c. Units:				
Inches Centimeters	(₁)			

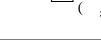
11. Hip (standing, at fullest part of		17. Acanthosis nigricans (check only one):		
measurements until you have within 4 in (10.2 cm) of each o		Absent (not detectable on close inspection,)(0
a. Circumference, 1st measure	ement:	Present (clearly present on close inspection, not visible to casual observer,	,	
hip	circumference	extent not measurable)	(1)
b. Circumference, 2nd measur	_ <u>•</u>	Mild (limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth)	(2)
	circumference	,	(2/
c. Units: Inches	(1)	Moderate (extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front)	(3)
Centimeters 12. Temperature (Oral)	(2)	Severe (extending anteriorly, > 6 inches in breadth, visible from front)	. (4)
12. Temperature (<i>Oral</i>)		, , ,	`	4/
a. Degrees:	_ <u>•</u>	18. Other skin abnormality (check all that appl	(y)	
		a. Jaundice:	(1)
b. Scale:	()	b. Palmar erythema:	(1)
Fahrenheit Centigrade	$\begin{pmatrix} & & & & & & & & & & & \\ & & & & & & & $	c. Spider angiomata:	(1)
Centigrade	(2)	d. Striae:	(1)
13. Blood pressure		e. Skin lesions:	(1)
a. Systolic:		f. Other (specify):	(1)
b. Diastolic:		g. None of the above:	(1)
14. Resting radial pulse:		19. Head, eyes, ears, nose, throat:		
The results runting pulse.	beats/minute	Normal	(.)
15. Respiratory rate:	breaths/minute	Abnormal 20.	<u> </u>	را (2
C. Examination findings		specify abnormality		
16. Skin:		20. Neck:		
Normal	(1)		(,
	19.	Normal 21	(₁) _
Abnormal	(₂)	Abnormal	(2)
		specify abnormality		
		21. Lymphatic:		
		Normal	(1)
		Abnormal 22.	 (ا (2

specify abnormality

22. Chest and lungs:	
Normal	
Abnormal	

22	()
23.	(2)

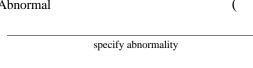






Normal		(
Abnormal		24. (₂)
	specify abnormality	

specify





Normal	(1)
A1	26.
Abnormal	(2)

25. Abdomen abnormality (check all that apply)

a. Ascites:	(1)
b. Obese:	(1)
c. Hepatomegaly: (if checked, span from right midclavio line):	cular (1)
	<u>•</u> _	

	CIII	
d. Splenomegaly:	(1)
e. Other (specify):	(1)

26. Extremities:

Normal	(1)
Abnormal	28. (₂)

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:

(Y	es 1)	(No) 2)
		31.	

3)

30. Was the patient able to swallow a placebo capsule (check only one):

E. Administrative information

32. Study Physician signature:

Yes, patient was able to swallow capsule	e (1)
No, patient was unable to swallow the	,	`
capsule	(jug)—	₂)
	<u> </u>	
Did not ask for a demonstration at this		

time

31. Study Physician PIN:	
--------------------------	--

35. Date form reviewed:		
	mon	year

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	t identific	cation	10. Waist (standing, at midpoint be of iliac crest and lowest part	tween highest point
1. Center ID:			repeat waist measurements u measurements within 4 in (10.2	ntil you have two
2. Patient ID:			a. 1st measurement:	•
3. Patient code:	_		b. 2nd measurement:	- — — —
4. Visit date:				- — • —
			c. Units:	
day	mon	year	Inches Centimeters	(₁)
5. Visit code:			2	2/
6. Form & revision:	_		11. Hip (standing, at fullest part of measurements until you have within 4 in (10.2 cm) of each o	two measurements
		•	a. 1st measurement:	
7. Study:		CyNCh 8		•
B. Measurements			b. 2nd measurement:	•
8. Height (shoes off)			c. Units:	
a. 1st measurement:			Inches	(1)
		•	Centimeters	$\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$
b. 2nd measurement:		<u> </u>	12. Temperature (oral)	
c. Units:			a. Degrees:	<u> </u>
Inches		(1)		
Centimeters		(2)	b. Scale:	
		_	Fahrenheit:	(1)
9. Weight (shoes off)			Centigrade:	(2)
a. 1st measurement:		•	13. Blood pressure	
b. 2nd measurement:			a. Systolic:	
		<u> </u>		mmHg
c. Units:		·	b. Diastolic:	
Pounds		(1)		mmHg
Kilograms		()		

Resting radial pulse: Respiratory rate:	beats/minute	D. Administrative information 18. Study Physician ID:
Liver signs	breaths/minute	19. Study Physician signature:
Liver and spleen:		
Normal	(1)	20. Clinical Coordinator ID:
Abnormal	18. (₂)	21. Clinical Coordinator signature:
Abnormality (check all that ap	pply)	
a. Ascites:	(1)	
b. Asterixis:	(1)	22. Date form reviewed:
c. Contractures:	(1)	
d. Fetor:	(1)	day mon year
e. Hepatomegaly:	(1)	
If Yes, span from right mide	lavicular line:	
If Yes, span from right mide	elavicular line:	
If Yes, span from right mide f. Jaundice:	<u> </u>	
f. Jaundice:	cm (₁)	
f. Jaundice: g. Muscle wasting:	cm (1) (1)	
f. Jaundice: g. Muscle wasting: h. Palmar erythema:	cm (1) (1) (1)	
f. Jaundice: g. Muscle wasting: h. Palmar erythema: i. Pedal edema:	cm (1) (1) (1) (1)	

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

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

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

Respondent: Parent of teens, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #8, Instructions for Pediatric Quality of Life (Forms PQ and PR) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Center, patient, and visit identification			B. Administrative information (To be completed by Clinical Coordinator after								
1.	. Center ID:			survey is completed.)							
2.	Patient ID:		8.	How was the Pediatric Quali questionnaire completed:	ty of Life						
3.	Patient code:			Calf administrant in English		`					
4.	Date form completed:			Self-administered in English Self-administered in Spanish Interview in English	*	1) 2) 3)					
	day mon	year		Interview in Spanish	(4)					
5.	Visit code:		9.	Clinical Coordinator a. PIN:b. Signature:							
6.	Form & revision:	<u>p q 1</u>		<u> </u>							
7.	Study:	CyNCh 8	10.	Date form reviewed:							
				day mon	year						

İ	Affix label here
ļ	Patient ID:
	Patient code:
ļ	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 FU	NCTIONING (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. Participa	ting in sports activity or exercise:	0	1	2	3	4
14. Lifting so	mething heavy:	0	1	2	3	4
15. Taking a	bath or shower by him or herself:	0	1	2	3	4
16. Doing ch	ores around the house:	0	1	2	3	4
17. Having h	urts or aches:	0	1	2	3	4
18. Low ener	rgy level:	0	1	2	3	4

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

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

PedsQI 4.0 - Parent (13-17)

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

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

Thank you for completing this questionnaire.

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

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

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

Respondent: Parent of child, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The parent should meet with the Clinical Coordinator and should be trained in completion of the form. Give the parent Flash Card #8, Instructions for Pediatric Quality of Life (Forms PQ and PR) and review the instructions with the parent. The parent should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the parent leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	enter, patient, and visit identi	fication	B. Administrative information (To be completed by Clinical Coordinator after						
1.	Center ID:		survey is completed.)						
2.	Patient ID:		8. How was the Pediatric Quality of Life questionnaire completed:						
3.	Patient code:		Calf administration Forelish	(`				
4.	Date form completed:		Self-administered in English Self-administered in Spanish Interview in English	(1) 2) 3)				
			Interview in Spanish	(4)				
	day mon	year	0 01 10 1						
5.	Visit code:		9. Clinical Coordinator a. PIN:						
6.	Form & revision:	<u>p r 1</u>	b . Signature:						
7.	Study:	CyNCh 8	10. Date form reviewed:						
			day mon y	ear					
			uu y IIIOII y	Cui					

Affix lal	bel 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

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

PedsQI 4.0 - Parent (8-12)

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

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

Thank you for completing this questionnaire.

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

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

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

Respondent: Patient, age 8-12.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #7, Instructions for Pediatric Quality of Life (Forms PW and PY) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	enter, patient, and visit identifica	tion	B. Administrative information (To be completed by Clinical Coordinator after	
1.	Center ID:		survey is completed.)	
2.	Patient ID:		8. How was the Pediatric Quality of Life questionnaire completed:	
3.	Patient code:		Self-administered in English ()
4.	Date form completed:		Self-administered in English Self-administered in Spanish (Interview in English Interview in Spanish (1) 2) 3)
	day mon	year	interview in Spainsii (4)
5.	Visit code:		9. Clinical Coordinatora. PIN:b. Signature:	
6.	Form & revision: p	<u>w</u> 1	b. Signature.	
7.	Study:	CyNCh 8	10. Date form reviewed:	
			dav mon vear	

Affix label he	re
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

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Patient ID: Patient code: Visit code:	Affix label here	İ
	Patient ID:	i
Visit code:	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 f	forget things:	0	1	2	3	4
31.	have trouble keeping up with my schoolwork:	0	1	2	3	4
32. I r	miss school because of not feeling well:	0	1	2	3	4
33. I r	miss school to go to the doctor or hospital:	0	1	2	3	4

Thank you for completing this questionnaire.

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

Purpose: To obtain the patient's quality of life.

When: Visits s, f52, and f76.

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

Respondent: Patient, age 13-17.

Instructions: The Clinical Coordinator should complete section A below and attach a label to pages 2-3. The patient should meet with the Clinical Coordinator and should be trained in completion of the form. Give the patient Flash Card #7, Instructions for Pediatric Quality of Life (Forms PY and PW) and review the instructions with the patient. The patient should then complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B. The NASH CRN has contracted with the PedsQLTM creators to use their forms in NASH CRN studies. These forms should not be used or copied for non NASH CRN purposes.

A. Ce	enter, patient, and visit identific	ation	B. Administrative information (To be completed by Clinical Coordinator after							
1.	Center ID:		survey is completed.)							
2.	Patient ID:		8. How was the Pediatric questionnaire complet	-						
3.	Patient code:		0.10 1 1 1 7	1.1	,					
4.	Date form completed:		Self-administered in E Self-administered in S Interview in English	·	1) 2) 3)					
			Interview in Spanish	(4)					
	day mon	year	0 01'0' 1 0 0 0 1' 0 1 0							
5.	Visit code:		9. Clinical Coordinator a. PIN:							
6.	Form & revision:	<u>y</u> 1	b . Signature:							
7.	Study:	CyNCh 8	10. Date form reviewed:							
			day	mon year						
			uay	mon year						

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

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

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

ABOUT	MY HEALTH AND ACTIVITIES (problems with)	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.	hurt or ache:	0	1	2	3	4
18.	have low energy:	0	1	2	3	4

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

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

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

ABOUT SCHOOL (problems with)		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.

RG - Registration

Purpose: To register patient as candidate for enrollment in CyNCh and to assign a patient ID number. This is the first form completed for a CyNCh patient. The Registration Form must be the first form keyed, before any other CyNCh forms.

When: At first screening visit (s). Administered by: Clinical Coordinator.

Respondent: Patient and guardian.

Instructions: Use Flash Cards as instructed. Do not assign a new ID if patient has previously been assigned an ID for a NASH CRN study. If is checked for any item, the patient is not eligible for CyNCh and the form should not be keyed.

A. Center, patient and visit	identification	10. Ha
1. Center ID:		Y
2. Patient ID:		N
3. Patient code:		N N
4. Visit date:		C. Info
day day	mon year	11 D
5. Visit code:	_S	11. Da
6. Form & revision:	<u>r g 1</u>	R

B. Consent

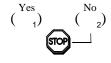
7. Study:

8. After reviewing the existing records (e.g., liver biopsy, elevated aminotransferases, and/or history) does the study physician feel that the patient may be suitable for the study:



CyNCh_8_

9. Has the patient (or patient's guardian) signed the CyNCh informed consent statement:

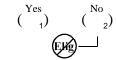


10. Has the patient signed the CyNCh informed assent statement:

Yes	(1)
No	(2)
	STOP —
Not using assent	(3)
Not using assent for this age child	$\begin{pmatrix} & & \\ & & 4 \end{pmatrix}$

C. Information about patient

13. Is the patient's age at least 8 years old and less than 18 years:



14. Gender:

Male (1)
Female (2)

15. Ethnic category (show the patient/guardian Flash Card #1 and ask the respondent to pick the category that describes the patient best; check only one):

Hispanic or Latino or Latina (1)

Not Hispanic, not Latino, not Latina (2)

16.	What describes the patient's Hispanic, Latino, or Latina origin best (show t tient/guardian Flash Card #1 and ask the dent to pick the subcategory that best desc patient's Hispanic, Latino, or Latina orig only one):	e resp cribes	20. Combined annual income before taxes of all members of patient's household (show guard ian Flash Card #4 and ask respondent to pick the category that describes the patient's combine household income best; check only one):	ie ed			
	Mexican	(1)			1)		
	Puerto Rican	(2) 3)		2)		
	Cuban	(3)		
	South or Central American	$\tilde{}$	3) 4)	\$50,000 or more (₄)		
	Other Spanish culture or origin	(₅)	D. Previous registration in a NASH CRN study			
	specify			21. Has the patient ever been assigned an ID number in a NASH CRN study:			
17.	Racial category (show the patient/guardi Card #2 and ask the respondent to pick gory or categories that describe the pati check all that apply)	the c	ate-	Yes (No 25.	2)		
	a. American Indian or Alaska Native:	(1)	22. In which NASH CRN studies has the			
	b. Asian:	(1)	patient previously been registered (check all the apply)	ıt		
	c. Black, African American, Negro, or			a. NAFLD Database: (1)		
	Haitian:	(1)	b. TONIC:	1)		
	d. Native Hawaiian or other Pacific Islander:	(1)	c. NAFLD Pediatric Database 2:	1)		
	e. White:f. Patient/guardian refused:		1)	d. Other, (specify):	1)		
			1)	specify	_		
18.	In what country was the patient born (ch one):	eck o	only	23. ID Number previously assigned to patient (recorpatient ID in item 2):	·d		
	Continental US (includes Alaska) or			patient 1D in tiem 2).			
	Hawaii	(1)				
	Other, (specify):	(2)	24. Code previously assigned to patient (record potient code in item 3):	<i>1</i> -		
	specify				_		
19.	Patient's current grade level in school (or home school) (show the patient/guardic Card #3 and ask the respondent to pick gory that describes the patient best; if time, report grade entering in the fall; chone):	an Fl the c	ate- mer	E. ID assignment (If a STOP or ineligible condition was checked i section B, the patient is ineligible and a Patient II should not be assigned. If the patient was presented.	D e-		
	Grades 1 to 5	(1)	viously registered in a NASH CRN study, a new II number should not be assigned.)	υ		
	Grades 6-8	(₂)					
	Grades 9-12		$\begin{pmatrix} & 2 \\ & 3 \end{pmatrix}$		25. Place ID label below and record Patient ID in item 2 and patient code in item 3.		
	Other, (specify):	(4)	in item 2 and patient code in item 3.			
	specify			CCCC ####,zzz			

Patient	ID:	 	

F. Administrative information

26. Clinical Coordinator PIN: ____ ___

27. Clinical Coordinator signature:

28. Date form reviewed:

day mon year

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 so 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:
- <u>r</u> <u>z</u> ___
- **6.** Form & revision:
- <u>r z 1</u>

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:



9. Is the patient's diabetes poorly controlled (HbA1c greater than 9% within the past 90 days):



C. Alcohol use exclusions

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



11. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her (*past and current*) alcohol intake:



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



D. Laboratory test exclusions

13. Hepatic Decompensation

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



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



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



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



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



f. Is the patient's white blood cell count less than 3,500 cells/mm³:



g. Is the patient's platelet count less than 130,000 cells/mm³:



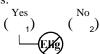
h. Is the patient's neutrophil count less than 1,500 cells/mm³:



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



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



E. Medication use exclusions

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



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



16. Initiation of any new medication/vitamin or supplement to treat NAFLD/NASH in the time period following liver biopsy and prior to randomization:



F. Other chronic liver disease exclusions

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



18. Does the patient have Wilson's disease defined by ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



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



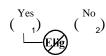
20. Does the patient have a transferrin saturation greater than 45% with histological evidence of iron overload (3+ or 4+ stainable iron on liver biopsy):



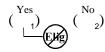
- **21.** Do any of the patient's assessments show evidence of other chronic liver disease
 - **a.** Suspected or proven liver cancer:



b. Hepatitis B (HBsAg):



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

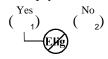


d. Any other type of liver disease other than NASH that warrants exclusion from the trial:



G. Liver biopsy exclusions

22. Inability to safely undergo a liver biopsy:



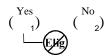
23. Biopsy out of window and patient chose not to repeat:



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



25. Local pathologist did not find NAFLD:



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



H. Other medical exclusions

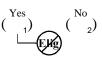
27. History of bariatric surgery or plans to have bariatric surgery during the CyNCh trial:



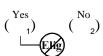
28. Inflammatory bowel disease (if active) or prior resection of small intestine:



29. Active coagulopathy:



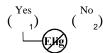
30. Active seizure disorders:



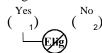
31. Gastrointestinal ulcers or other GI bleeding:



32. Renal dysfunction with a creatinine clearance of less than 90 mL/min/m²:



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



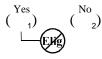
34. History of heart disease (myocardial infraction, heart failure, unstable arrhythmias):



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



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



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



38. Other conditions which, in the opinion of the investigator, would impede compliance or hinder completion of the study:



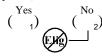
I. Birth control exclusion

39. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient (female of childbearing potential) willing to use effective birth control methods to avoid pregnancy during the 52 weeks of treatment (check "Yes" if patient is male or not of childbearing potential):



J. Check on ability to swallow study medication

40. In your judgment (Study Physician/Clinical Coordinator), is the patient able to swallow the CyNCh study medications (*if you are unsure, you may ask the patient to swallow an empty capsule*):



K. 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:

b. Weight in kilograms:



c. Weight group:

Less than or equal to 65kg

Greater than 65 - 80kg

(2

Greater than 80kg (3)

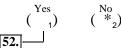
43. Based on today's physical examination, does the patient feel well today:



*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

L. Eligibility check on day of randomization

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



*Key forms RG, AD, BH, BP, CG, HF, LP, LR, LS, MR, ND, PE, PQ/PR, PW/PY, and SD. Run the Randomization Task on your clinic data system.

Patient	ID:		

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

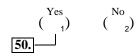
Yes

No
Task not run because patient is

Task not run because patient is known to be ineligible



46. Is the patient male:



47. Is the patient of childbearing potential:



*Administer pregnancy test.

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



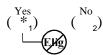
*Go to item 52.

49. Is the patient currently breast feeding

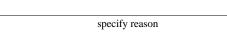


*Go to item 52.

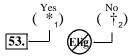
50. In the Study Physician's judgment, is there any reason to exclude the patient from randomization:



*If Yes, specify reason and then go to item 52:



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



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

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

RZ - Randomization Checks

Purpose: To check eligibility for CyNCh with respect to items not checked elsewhere on CyNCh screening forms and record reasons for ineligibility for patients found to be ineligible.

When: Visit rz.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: This form may be initiated at any time. If the patient proceeds to randomization, it must be reviewed on the day of randomization. Patients of childbearing potential must complete the randomization day pregnancy test at the clinic on the day of randomization. Height and weight must be obtained on the day of randomization.

If \mathfrak{S} is checked for any item, complete the entire form, but note that the patient may not participate in the CyNCh trial. If an item has not been assessed because the patient is ineligible, write " \mathbf{m} " (missing) next to that item. This form must be keyed for each patient for whom form RG was completed.

A. Center, patient, visit, and study identification

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

_		
day	mon	year

- **5.** Visit code: <u>r</u> <u>z</u> ____
- **7.** Study: CyNCh <u>8</u>

B. Diabetes Status

8. In the judgment of the Study Physician and based on the patient's medical history and laboratory results, does the patient have diabetes:



9. Is the patient's diabetes poorly controlled (HbA1c greater than 9% within the past 90 days):



C. Alcohol use exclusions

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



11. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient reliably quantify his/her (past and current) alcohol intake:



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



D. Laboratory test exclusions

13. Hepatic Decompensation

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



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



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



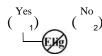
d. Is the patient's total bilirubin greater than 3 mg/dL:



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



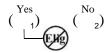
f. Is the patient's white blood cell count less than 3,500 cells/mm³:



g. Is the patient's platelet count less than 130,000 cells/mm³:



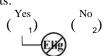
h. Is the patient's neutrophil count less than 1,500 cells/mm³:



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



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



E. Medication use exclusions

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



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



16. Initiation of any new medication/vitamin or supplement to treat NAFLD/NASH in the time period following liver biopsy and prior to randomization:



F. Other chronic liver disease exclusions

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



18. Does the patient have Wilson's disease defined by ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



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



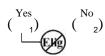
20. Does the patient have a transferrin saturation greater than 45% with histological evidence of iron overload (3+ or 4+ stainable iron on liver biopsy):



- **21.** Do any of the patient's assessments show evidence of other chronic liver disease
 - **a.** Suspected or proven liver cancer:



b. Hepatitis B (HBsAg):



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

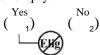


d. Any other type of liver disease other than NASH that warrants exclusion from the trial:



G. Liver biopsy exclusions

22. Inability to safely undergo a liver biopsy:



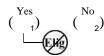
23. Biopsy out of window and patient chose not to repeat:



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



25. Local pathologist did not find NAFLD:



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



H. Other medical exclusions

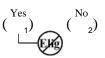
27. History of bariatric surgery or plans to have bariatric surgery during the CyNCh trial:



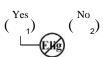
28. Inflammatory bowel disease (if active) or prior resection of small intestine:



29. Active coagulopathy:



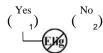
30. Active seizure disorders:



31. Gastrointestinal ulcers or other GI bleeding:



32. Renal dysfunction with a creatinine clearance of less than 90 mL/min/m²:



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



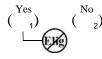
34. History of heart disease (myocardial infraction, heart failure, unstable arrhythmias):



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



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



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

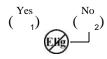


38. Other conditions which, in the opinion of the investigator, would impede compliance or hinder completion of the study:



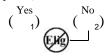
I. Birth control exclusion

39. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient *(female of childbearing potential)* willing to use effective birth control methods to avoid pregnancy during the 52 weeks of treatment *(check "Yes" if patient is male or not of childbearing potential):*



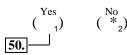
J. Check on ability to swallow study medication

40. In your judgment (Study Physician/Clinical Coordinator), is the patient able to swallow the CyNCh study medications (*if you are unsure, you may ask the patient to swallow an empty capsule*):



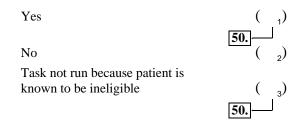
K. Eligibility check on day of randomization

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



*Key forms RG, AD, BH, BP, CG, HF, LP, LR, LS, MR, ND, PE, PQ/PR, PW/PY, and SD. Run the Randomization Task on your clinic data system.

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

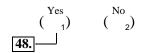


43. Based on today's physical examination, does the patient feel well today:

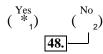


*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

44. Is the patient male:



45. Is the patient of childbearing potential:



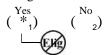
*Administer pregnancy test.

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



*Go to item 50.

47. Is the patient currently breast feeding



*Go to item 50.

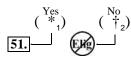
48. In the Study Physician's judgment, is there any reason to exclude the patient from randomization:



*If Yes, specify reason and then go to item 50:

specify reason

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



*Go to item 51 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.

†Complete items 50 and 53-57 and key the form. The form must be keyed to document the reasons for ineligibility for CyNCh.

L. Reasons for ineligibility for ineligible patients

Note: Complete this section for ineligible patients only.

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

a. Reason covered in items 9-49:	*	1))
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b. Other reason not covered on this form (specify):



*Go to item 53

Μ.	Physical	Examinat	ion (<i>must</i>	be	done	on	the	day
	of randon	nization)						

51. Height (shoes off)

a. 1st measurement:		
	•	

b. 2nd measurement:

c. Units:

Inches

Centimeters

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
C + 1 001	(

Greater than 80kg

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.):

		<u></u>
day	mon	year