Keyed: ( )

TONIC

BC - Blood Collection for DNA

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

When: Visit s2, rz, and as needed during followup. You can complete only one BC form prior to randomization. If a redraw of blood is necessary prior to randomization, revise the existing BC form to reflect the most recent blood draw for DNA banking. If redraw is necessary on the day of randomization, complete the BC form with visit code rz but hold the form for keying until after the patient has been randomized (you will not be able to key the form until after the patient has been randomized). If redraw is done after randomization or if the initial draw for DNA is done after randomization (eg, a patient who previously refused consent changes their mind to allow DNA banking), use the visit code for the followup visit whose time window is open. If redraw is done so soon after randomization that a followup visit window is not open, use visit code n.

By whom: Clinical Coordinator and laboratory personnel responsible for collection of whole blood.

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

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: b c 1

7. Study: TONIC_3

B. Check on consent

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

Yes (1) No (* 2)

STOP

** You cannot proceed until you get consent.*

9. Did the patient previously provide blood for DNA banking in the NAFLD Database:

Yes (1) No (2)

15.

C. Specimen for Genetics Repository

Attach ID labels to two 10mL EDTA tubes and fill each with whole blood; invert each tube gently 6 times to mix blood with additives; keep tubes at room temperature until the same day shipment to the NIDDK Genetics Repository.

10. Was blood collected for the NIDDK Genetics Repository:

Yes (1)

11.

No, *(specify):* (2)

_____
specify

15.

11. Date and time of blood draw

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

b. Time:

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

12. Number of 10 mL EDTA tubes: ____

13. Form copy of tube labels:

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

14. Phlebotomist:

_____
print name

D. Administrative information

15. Clinical Coordinator PIN: ____ ____ ____

16. Clinical Coordinator signature:

_____

17. Date form reviewed:

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

TONIC

BG - Baseline History

Purpose: To collect baseline history information about the patient.
When: Visit s1.
Administered by: Clinical Coordinator, reviewed by Study Physician.
Respondent: Patient or patient's parent.
Instructions: Collect information by interview or chart review. If C is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for TONIC. If EXC is checked for an item, the patient is ineligible and cannot enroll in TONIC. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

A. Center, visit, and patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: s 1 ____ ____

6. Form & revision: b g 1

7. Study: TONIC 3

B. Family history

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

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

10.

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

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

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

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

12.

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

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

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

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

13. Do any of the patient's first degree relatives (parent, brother, sister) have obesity:

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

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

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

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

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

C. NAFLD history

16. Date patient was first diagnosed with nonalcoholic fatty liver disease (NAFLD):

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

17. What prompted the evaluation for NAFLD *(check all that apply)*

a. Symptoms for liver disease: (1)

b. Result of being evaluated for another illness: (1)

c. During a routine or insurance physical examination: (1)

d. Blood donation: (1)

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

_____
specify

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

a. Liver biopsy: (1)

b. Imaging studies *(Ultrasound, CT, MRI):* (1)

c. Elevated aminotransferases: (1)

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

_____
specify

D. Weight history

19. What was the patient's birthweight:

____ ____–____ ____
lbs oz

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

E. Tobacco cigarette smoking history

(interview with patient; not by chart review)

23. Have you ever smoked tobacco cigarettes:

Never (1)
28.

In the past but not anymore (2)

Currently smokes cigarettes (3)

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

Yes (1) No (2)
28.

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

____ ____
years

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

____ ____
years

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

____ ____ ____
cigarettes/day

F. Menstrual history

28. Is the patient female:

Yes (1) No (2)
31.

29. Menarche history

a. Has menarche occurred:

Yes (1) No (2)
31.

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

____ ____
age in years

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

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

G. Medical history *(⚠C means Caution; condition is exclusionary if study physician agrees with diagnosis)*

31. Has the patient ever been diagnosed with or treated for any of the following *(check all that apply; source of information can be interview and/or chart review)*

a. Diabetes type 1: ⚠C (1)
b. Diabetes type 2: ⚠C (1)
c. Gestational diabetes *(diabetes of pregnancy):* (1)
d. Hepatitis B: ⚠C (1)
e. Hepatitis C: ⚠C (1)
f. Autoimmune hepatitis: ⚠C (1)
g. Autoimmune cholestatic liver disorder (PBC or PSC): ⚠C (1)
h. Wilson's disease: ⚠C (1)
i. Alpha-1-antitrypsin (A1AT) deficiency: ⚠C (1)
j. Hemochromatosis or iron overload: ⚠C (1)
k. Drug induced liver disease: ⚠C (1)
l. Gilbert's syndrome: (1)
m. Esophageal or gastric varices on endoscopy: ⚠C (1)
n. Bleeding from varices: ⚠C (1)
o. Other gastrointestinal bleeding: (1)
p. Biliary diversion: ⚠C (1)
q. Metabolic acidosis: ⚠C (1)
r. Ascites: ⚠C (1)
s. Edema: (1)
t. Hepatic encephalopathy: ⚠C (1)
u. Portal hypertension: ⚠C (1)
v. Hepatorenal syndrome: ⚠C (1)
w. Hepatopulmonary syndrome: ⚠C (1)
x. Short bowel syndrome: ⚠C (1)
y. Hemophilia *(bleeding disorder):* ⚠C (1)
z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)
aa. Endocrine disease *(hormonal abnormality):* (1)
ab. Hepatocellular carcinoma: ⚠C (1)
ac. Other malignancy *(cancer):* ⚠C (1)
ad. Human immunodeficiency virus (HIV): ⚠C (1)
ae. Peripheral neuropathy: (1)
af. Seizure disorder or epilepsy: (1)
ag. Drug allergies: (1)
ah. Hypothyroidism: (1)
ai. Hypertension: (1)
aj. Cerebrovascular disease: (1)
ak. Dysbetalipoproteinemia: ⚠C (1)

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

am. Pancreatitis: (1)

an. Cholelithiasis: (1) C

ao. Coronary artery disease: (1) C

ap. Congestive heart failure: (1) C

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

ar. Kidney disease: (1) C

as. Polycystic ovary syndrome: (1)

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

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (1)

ax. Major depression: (1)

ay. Schizophrenia: (1)

az. Bipolar disorder: (1)

ba. Obsessive compulsive disorder: (1)

bb. Severe anxiety or personality disorder: (1)

bc. Substance abuse: (1) C

bd. None of the above: (1)

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

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

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

c. Biliopancreatic diversion: (1) C

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

_____

e. None of the above: (1)

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

Yes (1) Elig No (2)

34. Has the patient received total parenteral nutrition (TPN) in the past 3 years:

Yes (1) Elig No (2)

35. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) Elig No (2)

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

Yes (1) No (2)

H. Drugs historically associated with NAFLD

36. Has the patient used any tetracyclines, salicylates, or valproic acid in the past 2 years *(check all that apply)*

a. Acetylsalicylic acid (ASA): (1)

b. Aspirin - 325 mg: (1)

c. Demeclocycline (Declomycin): (1)

d. Divalproex (Depakote): (1)

e. Doxycycline (Monodox): (1)

f. Minocycline (Dynacin, Minocin): (1)

g. Oxytetracycline (Terramycin): (1)

h. Tetracycline (Achromycin): (1)

i. Valproate sodium (Depacon): (1)

j. Valproic acid (Depakene): (1)

k. Other known hepatotoxin *(specify):* (1)

_____

l. None of the above: (1)

37. Were any of the items in 36a-k checked:

Yes (* 1) C No (2)

**Caution: Use of any of these drugs for more than 2 consecutive weeks in the past 2 years is exclusionary.*

38. Has the patient taken any systemic corticosteroids in the past 2 years *(check all that apply):*

a. Betamethasone sodium (Celestone): (1)

b. Cortisol: (1)

c. Cortisone: (1)

d. Dexamethasone (Decadron): (1)

e. Hydrocortisone (Hydrocortone): (1)

f. Methylprednisolone (Solu-Medrol): (1)

g. Prednisolone (Prelone): (1)

h. Prednisone: (1)

i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (1)

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

_____

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

_____

l. None of the above: (1)

39. Were any of the items 38a-k checked:

Yes (* 1) C No (2)

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

40. Has the patient taken any anabolic steroids or tamoxifen in the past 2 years *(check all that apply)*

a. Boldenone undecylenate (Equipoise): (1)

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

c. Methandrostenolone (Dianabol): (1)

d. Methyltestosterone (Android): (1)

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

f. Oxandrolone (Oxandrin): (1)

g. Oxymetholone (Anadrol): (1)

h. Stanzolol (Winstrol): (1)

i. Tamoxifen (Nolvadex): (1)

j. Testosterone (Depo-Testosterone): (1)

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

_____

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

_____

m. None of the above: (1)

41. Were any of the items 40a-l checked:

Yes (* 1) C No (2)

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

I. Use of antidiabetic drugs

42. Does the patient have a known intolerance to metformin:

( ) Yes 1 → Elg ( ) No 2

43. Has the patient used any antidiabetic medications in the past 3 months *(check all that apply):*

a. Acarbose (Precose): (1)
b. Acetohexamide (Dymelor): (1)
c. Chlorpropamide (Diabinese): (1)
d. Glimepiride (Amaryl): (1)
e. Glipizide (Glucotrol, Glucatrol XL): (1)
f. Glyburide (Micronase, DiaBeta, Glynase): (1)
g. Insulin: (1)
h. Metformin (Glucophage, Glucophage XR): (1)
i. Miglitol (Glycet): (1)
j. Nateglinide (Starlix): (1)
k. Pioglitazone (Actos): (1)
l. Repaglinide (Prandin): (1)
m. Rosiglitazone (Avandia): (1)
n. Tolazamide (Tolinase): (1)
o. Tolbutamide (Orinase): (1)
p. Other, *(specify):* (1)

_____

q. None of the above: (1)

44. Were any of the items 43a-p checked:

(*) Yes 1 → C ( ) No 2

**Caution: Use of antidiabetic drugs in the 3 months prior to randomization is exclusionary.*

J. Use of antiNAFLD drugs and vitamins

45. Has the patient taken any of these antiNAFLD drugs in the past 3 months *(check all that apply)*

a. Betaine (Cystadone): (1)
b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
c. Metformin: (1)
d. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)
e. S-Adenylmethionine (SAM-e): (1)
f. Milk thistle: (1)
g. Probiotics *(any form):* (1)
h. Gemfibrozil (Gen-Fibro, Lopid): (1)
i. None of the above: (1)

46. Were any of item 45a-h checked:

(*) Yes 1 → C ( ) No 2

**Caution: Use of antiNAFLD drugs in the 3 months prior to randomization is exclusionary.*

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

( ) Yes 1 ( ) No 2

48. Has the patient taken any vitamin E (either as a supplement or in a multivitamin) in the past 3 months:

( ) Yes 1 ( ) No 2 → 50.

49. Was/Is the dose of vitamin E greater than 100 IU/day:

(*) Yes 1 → C ( ) No 2

**Caution: Use of vitamin E at more than 100 IU/day in the 3 months prior to randomization is exclusionary.*

50. Is the patient willing to refrain from taking vitamin E in amounts greater than 100 IU/day during TONIC:

( ) Yes (1) ( ) No (*2) → Elig

**Patient may not take vitamin E supplements at doses greater than 100 IU/day during TONIC.*

51. Does the patient have a known intolerance to vitamin E:

( ) Yes (1) → Elig ( ) No (2)

52. What other vitamins (other than multivitamins and vitamin E) has the patient taken in the past 3 months *(check all that apply):*

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

b. Vitamin C: ( ) (1)

c. Vitamin D: ( ) (1)

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

_____

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

K. Use of statins, fibrates, and antiobesity drugs

53. Has the patient taken any lipid lowering medications in the past 3 months *(check all that apply):*

a. Atorvastatin (Lipitor): ( ) (1)

b. Colestipol hydrochloride (Colestid): ( ) (1)

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

d. Fenofibrate (Tricor): ( ) (1)

e. Fluvastatin sodium (Lescol): ( ) (1)

f. Lovastatin (Mevacor): ( ) (1)

g. Nicotinic acid (Niaspan): ( ) (1)

h. Pravastatin sodium (Pravachol): ( ) (1)

i. Rosuvastatin (Crestor): ( ) (1)

j. Simvastatin (Zocor): ( ) (1)

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

_____

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

54. Has the patient taken any antiobesity medications in the past 3 months *(check all that apply):*

a. Dexfenfluramine hydrochloride (Redux): ( ) (1)

b. Fenfluramine hydrochloride (Pondimin): ( ) (1)

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

d. Orlistat (Xenical): ( ) (1)

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

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

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

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

_____

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

_____

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

55. Were any of the items 54a-i checked:

( ) Yes (*1) → C ( ) No (2)

**Caution: Use of antiobesity medications in the 3 months prior to randomization is exclusionary.*

L. Use of other medications and supplements

56. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 3 months *(check all that apply):*

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

_____

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

_____

i. None of the above: (1)

57. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 3 months *(check all that apply):*

a. Cimetidine (Tagamet): (1)
b. Esomeprazole magnesium (Nexium): (1)
c. Famotidine (Pepcid): (1)
d. Lansoprazole (Prevacid): (1)
e. Nizatidine (Axid): (1)
f. Omeprazole (Prilosec): (1)
g. Ranitidine (Zantac): (1)
h. Ranitidine bismuth citrate (Tritec): (1)
i. Antacids, *(specify):* (1)

_____

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

_____

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

_____

l. None of the above: (1)

58. Has the patient taken any allergy or asthma medications in the past 3 months that have not already been reported on this form *(check all that apply)*

a. Albuterol: (1)
b. Beclomethasone dipropionate (Beclovent, Vanceril): (1)
c. Budesonide (Pulmicort, Rhinocort): (1)
d. Fluticasone propionate (Flonase, Flovent): (1)
e. Loratadine (Claritin): (1)
f. Mometasone furoate (Nasonex): (1)
g. Triamcinolone acetonide (Azmacort, Nasacort): (1)
h. Other, *(specify):* (1)

_____

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

_____

j. None of the above: (1)

59. Has the patient taken any supplements in the past 3 months that have not already been reported on this form *(check all that apply)*

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

_____

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

_____

z. None of the above: (1)

60. Has patient taken any of the following medications in the past 3 months *(check all that apply)*

a. Isotretinoin (Accutane): (1)
b. Levonorgestrel (Norplant): (1)
c. Levothyroxine (Levoxyl, Synthroid): (1)
d. Liothyronine (Cytomel): (1)
e. Oral contraceptives: (1)
f. Penicillamine (Cuprimine, Depen): (1)
g. Trientine hydrochloride (Syprine): (1)
h. Other, *(specify):* (1)

_____

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

_____

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

_____

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

_____

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

_____

m. None of the above: (1)

M. Willingness to use effective birth control methods

61. Are you female and of childbearing potential:

Yes (1) No (2)
65.

62. Are you currently pregnant:

Yes (1) No (2)
Elig

63. Are you currently breast feeding:

Yes (* 1) No (2)
C

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

64. Are you willing to use effective birth control methods during TONIC:

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

N. Administrative information

65. Study Physician PIN: ____ ____ ____

66. Study Physician signature:

_____

67. Clinical Coordinator PIN: ____ ____ ____

68. Clinical Coordinator signature:

_____

69. Date form reviewed:

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

TONIC

BG - Baseline History

Purpose: To collect baseline history information about the patient.
When: Visit s1.
Administered by: Clinical Coordinator, reviewed by Study Physician.
Respondent: Patient or patient's parent.
Instructions: Collect information by interview or chart review. If ⚠C is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for TONIC. If ⊘EXC is checked for an item, the patient is ineligible and cannot enroll in TONIC. The form should not be keyed to the data system, but the form should be retained; set aside with forms for other patients who started screening, but were found to be ineligible.

A. Center, visit, and patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: s 1 ____ ____

6. Form & revision: b g 2

7. Study: TONIC 3

B. Family history

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

Yes (1) No (2)
10.

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

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

_____
specify

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

Yes (1) No (2)
12.

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

Yes (1) No (2)

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

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

13. Do any of the patient's first degree relatives (parent, brother, sister) have obesity:

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

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

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

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

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

C. NAFLD history

16. Date patient was first diagnosed with nonalcoholic fatty liver disease (NAFLD):

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

17. What prompted the evaluation for NAFLD *(check all that apply)*

a. Symptoms for liver disease:	(1)
b. Result of being evaluated for another illness:	(1)
c. During a routine or insurance physical examination:	(1)
d. Blood donation:	(1)
e. Other *(specify):*	(1)

_____
specify

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

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

_____
specify

D. Weight history

19. What was the patient's birthweight:

____ ____–____ ____
lbs oz

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

E. Tobacco cigarette smoking history

(interview with patient; not by chart review)

23. Have you ever smoked tobacco cigarettes:

Never	(1)
	28. ⌊
In the past but not anymore	(2)
Currently smokes cigarettes	(3)

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

Yes (1) No (2)

28. ⌊

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

____ ____
years

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

____ ____
years

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

____ ____ ____
cigarettes/day

F. Menstrual history

28. Is the patient female:

(Yes 1) (No 2)

31.

29. Menarche history

a. Has menarche occurred:

(Yes 1) (No 2)

31.

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

____ ____
age in years

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

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

G. Medical history *(C means Caution; condition is exclusionary if study physician agrees with diagnosis)*

31. Has the patient ever been diagnosed with or treated for any of the following *(check all that apply; source of information can be interview and/or chart review)*

a. Diabetes type 1:	C (1)
b. Diabetes type 2:	C (1)
c. Gestational diabetes *(diabetes of pregnancy):*	(1)
d. Hepatitis B:	C (1)
e. Hepatitis C:	C (1)
f. Autoimmune hepatitis:	C (1)
g. Autoimmune cholestatic liver disorder (PBC or PSC):	C (1)
h. Wilson's disease:	C (1)
i. Alpha-1-antitrypsin (A1AT) deficiency:	C (1)
j. Hemochromatosis or iron overload:	C (1)
k. Drug induced liver disease:	C (1)
l. Gilbert's syndrome:	(1)
m. Esophageal or gastric varices on endoscopy:	C (1)
n. Bleeding from varices:	C (1)

o. Other gastrointestinal bleeding: (1)

p. Biliary diversion: (1)
C

q. Metabolic acidosis: (1)
C

r. Ascites: (1)
C

s. Edema: (1)

t. Hepatic encephalopathy: (1)
C

u. Portal hypertension: (1)
C

v. Hepatorenal syndrome: (1)
C

w. Hepatopulmonary syndrome: (1)
C

x. Short bowel syndrome: (1)
C

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

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

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

ab. Hepatocellular carcinoma: (1)
C

ac. Other malignancy *(cancer):* (1)
C

ad. Human immunodeficiency virus (HIV): (1)
C

ae. Peripheral neuropathy: (1)

af. Seizure disorder or epilepsy: (1)

ag. Drug allergies: (1)

ah. Hypothyroidism: (1)

ai. Hypertension: (1)

aj. Cerebrovascular disease: (1)

ak. Dysbetalipoproteinemia: (1)
C

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

am. Pancreatitis: (1)

an. Cholelithiasis: (1)
C

ao. Coronary artery disease: (1)
C

ap. Congestive heart failure: (1)
C

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

ar. Kidney disease: (1)
C

as. Polycystic ovary syndrome: (1)

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

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (1)

ax. Major depression: (1)

ay. Schizophrenia: (1)

az. Bipolar disorder: (1)

ba. Obsessive compulsive disorder: (1)

bb. Severe anxiety or personality disorder: (1)

bc. Substance abuse: (1)
C

bd. None of the above: (1)

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

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

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

c. Biliopancreatic diversion: (1)
C

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

_____

e. None of the above: (1)

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

Yes (1) → Elig No (2)

34. Has the patient received total parenteral nutrition (TPN) in the past 3 years:

Yes (1) → Elig No (2)

35. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) → Elig No (2)

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

Yes (1) No (2)

H. Drugs historically associated with NAFLD

36. Has the patient used any tetracyclines, salicylates, or valproic acid in the past 2 years *(check all that apply)*

a. Acetylsalicylic acid (ASA): (1)

b. Aspirin - 325 mg: (1)

c. Demeclocycline (Declomycin): (1)

d. Divalproex (Depakote): (1)

e. Doxycycline (Monodox): (1)

f. Minocycline (Dynacin, Minocin): (1)

g. Oxytetracycline (Terramycin): (1)

h. Tetracycline (Achromycin): (1)

i. Valproate sodium (Depacon): (1)

j. Valproic acid (Depakene): (1)

k. Other known hepatotoxin *(specify):* (1)

_____

l. None of the above: (1)

37. Were any of the items in 36a-k checked:

Yes (*1) → C No (2)

**Caution: Use of any of these drugs for more than 2 consecutive weeks in the past 2 years is exclusionary.*

38. Has the patient taken any systemic corticosteroids in the past 2 years *(check all that apply):*

a. Betamethasone sodium (Celestone): (1)

b. Cortisol: (1)

c. Cortisone: (1)

d. Dexamethasone (Decadron): (1)

e. Hydrocortisone (Hydrocortone): (1)

f. Methylprednisolone (Solu-Medrol): (1)

g. Prednisolone (Prelone): (1)

h. Prednisone: (1)

i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (1)

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

_____

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

_____

l. None of the above: (1)

39. Were any of the items 38a-k checked:

Yes (*1) → C No (2)

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

40. Has the patient taken any anabolic steroids or tamoxifen in the past 2 years *(check all that apply)*

a. Boldenone undecylenate (Equipoise): (1)

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

c. Methandrostenolone (Dianabol): (1)

d. Methyltestosterone (Android): (1)

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

f. Oxandrolone (Oxandrin): (1)

g. Oxymetholone (Anadrol): (1)

h. Stanzolol (Winstrol): (1)

i. Tamoxifen (Nolvadex): (1)

j. Testosterone (Depo-Testosterone): (1)

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

_____

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

_____

m. None of the above: (1)

41. Were any of the items 40a-l checked:

Yes (*1) → C No (2)

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

I. Use of antidiabetic drugs

42. Does the patient have a known intolerance to metformin:

Yes (1) → Elig No (2)

43. Has the patient used any antidiabetic medications in the past 3 months *(check all that apply):*

a. Acarbose (Precose): (1)

b. Acetohexamide (Dymelor): (1)

c. Chlorpropamide (Diabinese): (1)

d. Glimepiride (Amaryl): (1)

e. Glipizide (Glucotrol, Glucatrol XL): (1)

f. Glyburide (Micronase, DiaBeta, Glynase): (1)

g. Insulin: (1)

h. Metformin (Glucophage, Glucophage XR): (1)

i. Miglitol (Glycet): (1)

j. Nateglinide (Starlix): (1)

k. Pioglitazone (Actos): (1)

l. Repaglinide (Prandin): (1)

m. Rosiglitazone (Avandia): (1)

n. Tolazamide (Tolinase): (1)

o. Tolbutamide (Orinase): (1)

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

_____

q. None of the above: (1)

44. Were any of the items 43a-p checked:

Yes (*1) → C No (2)

**Caution: Use of antidiabetic drugs in the 3 months prior to randomization is exclusionary.*

J. Use of antiNAFLD drugs and vitamins

45. Has the patient taken any of these antiNAFLD drugs in the past 3 months *(check all that apply)*

a. Betaine (Cystadone): (1)

b. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)

c. Metformin: (1)

d. Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol): (1)

e. S-Adenylmethionine (SAM-e): (1)

f. Milk thistle: (1)

g. Probiotics *(any form):* (1)

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

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

_____
specify

j. None of the above: (1)

46. Were any of item 45a-h checked:

Yes (*1) → C No (2)

**Caution: Use of antiNAFLD drugs in the 3 months prior to randomization is exclusionary.*

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

Yes (1) No (2)

48. Has the patient taken any vitamin E (either as a supplement or in a multivitamin) in the past 3 months:

Yes (1) No (2) → 50.

49. Was/Is the dose of vitamin E greater than 100 IU/day:

Yes (*1) → C No (2)

**Caution: Use of vitamin E at more than 100 IU/day in the 3 months prior to randomization is exclusionary.*

50. Is the patient willing to refrain from taking vitamin E in amounts greater than 100 IU/day during TONIC:

Yes (1) → Elig No (*2)

**Patient may not take vitamin E supplements at doses greater than 100 IU/day during TONIC.*

51. Does the patient have a known intolerance to vitamin E:

Yes (1) → Elig No (2)

52. What other vitamins (other than multivitamins and vitamin E) has the patient taken in the past 3 months *(check all that apply):*

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

b. Vitamin C: (1)

c. Vitamin D: (1)

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

_____

e. None of the above: (1)

K. Use of statins, fibrates, and antiobesity drugs

53. Has the patient taken any lipid lowering medications in the past 3 months *(check all that apply):*

a. Atorvastatin (Lipitor): (1)

b. Colestipol hydrochloride (Colestid): (1)

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

d. Fenofibrate (Tricor): (1)

e. Fluvastatin sodium (Lescol): (1)

f. Lovastatin (Mevacor): (1)

g. Nicotinic acid (Niaspan): (1)

h. Pravastatin sodium (Pravachol): (1)

i. Rosuvastatin (Crestor): (1)

j. Simvastatin (Zocor): (1)

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

_____

l. None of the above: (1)

54. Has the patient taken any antiobesity medications in the past 3 months *(check all that apply):*

a. Dexfenfluramine hydrochloride (Redux): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

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

d. Orlistat (Xenical): (1)

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

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

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

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

_____

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

_____

j. None of the above: (1)

55. Were any of the items 54a-i checked:

Yes (*1) No (2)

C

**Caution: Use of antiobesity medications in the 3 months prior to randomization is exclusionary.*

L. Use of other medications and supplements

56. Has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications in the past 3 months *(check all that apply):*

a. Acetaminophen (Tylenol): (1)

b. Aspirin - 325 mg: (1)

c. Celecoxib (Celebrex): (1)

d. Ibuprofen (Advil, Motrin): (1)

e. Indomethacin (Indocin): (1)

f. Naproxen (Aleve, Naprosyn): (1)

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

_____

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

_____

i. None of the above: (1)

57. Has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications in the past 3 months *(check all that apply):*

a. Cimetidine (Tagamet): (1)

b. Esomeprazole magnesium (Nexium): (1)

c. Famotidine (Pepcid): (1)

d. Lansoprazole (Prevacid): (1)

e. Nizatidine (Axid): (1)

f. Omeprazole (Prilosec): (1)

g. Ranitidine (Zantac): (1)

h. Ranitidine bismuth citrate (Tritec): (1)

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

_____

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

_____

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

_____

l. None of the above: (1)

58. Has the patient taken any allergy or asthma medications in the past 3 months that have not already been reported on this form *(check all that apply)*

a. Albuterol: (1)

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

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

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

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

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

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

_____

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

_____

j. None of the above: (1)

59. Has the patient taken any supplements in the past 3 months that have not already been reported on this form *(check all that apply)*

a. Alpha-lipoic acid: (1)

b. Beta-carotene: (1)

c. Calcium (any form): (1)

d. Carnitine (any form): (1)

e. Chondroitin (any form): (1)

f. Cod liver oil: (1)

g. Coenzyme Q: (1)

h. Dichloroacetate: (1)

i. Echinacea: (1)

j. Fish oil (any form): (1)

k. Flax seed oil: (1)

l. Garlic: (1)

m. Ginkgo biloba: (1)

n. Glucosamine (any form): (1)

o. Lecithin: (1)

p. Magnesium: (1)

q. N-acetyl-cysteine: (1)

r. Potassium (any form): (1)

s. Saw palmetto: (1)

t. Selenium: (1)

u. St. John's Wort: (1)

v. Taurine: (1)

w. Zinc picolinate: (1)

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

_____

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

_____

z. None of the above: (1)

60. Has patient taken any of the following medications in the past 3 months *(check all that apply)*

a. Isotretinoin (Accutane): (1)

b. Levonorgestrel (Norplant): (1)

c. Levothyroxine (Levoxyl, Synthroid): (1)

d. Liothyronine (Cytomel): (1)

e. Oral contraceptives: (1)

f. Penicillamine (Cuprimine, Depen): (1)

g. Trientine hydrochloride (Syprine): (1)

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

_____

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

_____

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

_____

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

_____

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

_____

m. None of the above: (1)

M. Willingness to use effective birth control methods

61. Are you female and of childbearing potential:

Yes (1) No (2)

65.

62. Are you currently pregnant:

Yes (1) No (2)

Elig

63. Are you currently breast feeding:

Yes (* 1) No (2)

C

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

64. Are you willing to use effective birth control methods during TONIC:

Yes (1) No (2)

Elig

N. Administrative information

65. Study Physician PIN: ____ ____ ____

66. Study Physician signature:

_____

67. Clinical Coordinator PIN: ____ ____ ____

68. Clinical Coordinator signature:

_____

69. Date form reviewed:

____ ____–____ ____ ____–____ ____

day mon year

TONIC

BP - Blood Processing for Plasma and Serum

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

When: Visits s2, f024, f048, f072, and f096.

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of whole blood.

Instructions: Put 2.7 mL of whole blood in CTAD tube and fill SST tubes with whole blood and prepare plasma and serum aliquots in the quantities specified below for the visit.

	Plasma:		**Serum:**	
Visit	No. of CTAD tubes	No. of plasma aliquots	No. of 10 mL SST tubes to fill	No. of serum aliquots
s2	1	2 or 3	4	40
f024	none	none	2	20
f048	1	2 or 3	4	40
f072	none	none	2	20
f096	1	2 or 3	4	40

Label CTAD and SST tubes of whole blood using labels specific for the patient and visit; these labels are generated by the clinic upon registration (screening labels) or after randomization (followup visit labels). Attach duplicate whole blood tube labels in items 11 and 13 below. Process blood for plasma and serum within two hours. After separation, prepare 2 or 3 aliquots of plasma, depending on volume of plasma obtained: transfer 0.5 mL of plasma to each of 2 or 3 (2.0 mL) cryovials. After separation, transfer 0.5 mL of serum to each of the 20 or 40 (2.0 mL) cryovials depending on the visit. Label the plasma and serum cryovials with the numbered patient-specific plasma (blue top) and serum (red top) cryovial labels provided by the DCC. Choose one of the cryovial label sets provided by the DCC for this patient for use with this visit. Affix serum aliquot #00 label (all visits) and plasma aliquot #00 label (if visit s2, f048, or f096) to this form in item 18. The LS code keyed from the cryovial labels in item 18 of this form links the cryovials collected today with the date and visit identified in items 4 and 5 of this form. Freeze labeled aliquots of plasma and serum immediately according to procedures specified in the TONIC SOP, Part I. **NOTE:** Immediately upon completion of plasma and serum aliquot preparation, destroy any left-over cryovial labels from the label set used at this visit; use of these cryovial labels at any other visit will result in aliquots from both visits being unusable since the visit at which they were collected will not be uniquely identified.

A. Center, patient and visit identification

1. Center code: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: b p 1

7. Study: TONIC 3

B. Processing whole blood

Plasma and serum aliquots are to be separated from whole blood per instructions in the SOP. Draw fasting blood in the morning.

8. Was blood collected for the NIDDK Biosample Repository:

Yes (1)
No, patient was not fasting for 12 hours (2)
23. ____
No, other reason *(specify):* (3)
23. ____

_____
specify other reason

9. Date and time of blood draw

a. Date:

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

b. Time:

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

10. Was blood collected for plasma banking at this visit *(plasma banking is required at visits s2, f048, and f096):*

Yes (1) No (2)
12. ____

11. Attach duplicate CTAD tube label:

TONIC Form. BP, Plas.
Pt: 9999, xyz
Visit vvvv
Date: _____

12. Number of SST serum separator (red-top) tubes *(4 tubes at visits s2, f048, and f096; 2 tubes at visits f024 and f072):*

____

13. Attach duplicate SST serum separator tube labels:

TONIC Serum 1
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

TONIC Serum 2
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

TONIC Serum 3
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

TONIC Serum 4
Pt: 9999, xyz
Visit: vvvv
BP
Date: _____

14. Phlebotomist:

_____
print name

C. Aliquots for plasma and serum

Pour 0.5 mL of plasma into each of up to three 2.0 mL pre-labeled cryovials and pour 0.5 mL of serum into each of forty 2.0 mL pre-labeled cryovials at visits s2, f048, and f096; 20 pre-labeled cryovials at visits f024 and f072.

15. Date and time of separation into plasma and serum aliquots

a. Date:

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

b. Time:

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

16. Number of aliquots of plasma *(if this was not a plasma banking visit, record "0")*:

____

17. Number of aliquots of serum: ____ ____

18. Attach duplicate cryovial labels
(use aliquot 00 labels which are located in the first row of labels for each label set):

Serum aliquot #00 label	Plasma aliquot #00 label

19. Technician:

_____
print name

D. Freezing aliquots

Freeze plasma and serum aliquots immediately at -70°C or -20°C. If frozen at -20°C, the cryovials must be transferred to -70°C within 24 hours. Batch ship monthly to the NIDDK BioSample Repository at Fisher BioServices.

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

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

b. Time:
____ ____:____ ____ (1) (2)
hour minute am pm

21. Number of cryovials frozen: ____ ____

22. Technician:

_____
print name

E. Administrative information

23. Clinical Coordinator PIN: ____ ____ ____

24. Clinical Coordinator signature:

_____

25. Date form reviewed:

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

TONIC

CG - Genetic Consent Documentation

Purpose: To document consent options selected for use of DNA samples for genetic research.
When: Visit s2 and as needed during followup (during followup, use the visit code of the followup visit that is open).
By whom: Study Physician and Clinical Coordinator.
Instructions: Complete this form based on the consent documents signed by the patient/parent. If the patient changes his/her mind regarding consent for use of samples after the initial form is completed, complete a new CG form.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date form completed:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: c g 1

7. Study: TONIC 3

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

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

(Yes 1) (No 2)

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

(Yes 1) (No 2)

10. Does the patient/guardian consent to future genetic research on liver disease, its complications, and metabolic disorders by this study or other study investigators:

(Yes 1) (No 2)

11. Other information related to consent for genetic research that clinic staff feel needs to be keyed to the study database *(e.g., if your genetic consent had other options that are not covered by the 3 categories of use of samples specified above):*

_____

_____

_____

_____

_____

12. In your judgment, has the patient/parent consented to collection of blood for DNA banking *(this question is asked in recognition that not all IRBs will have approved consent statements that include language that can be mapped into the questions in items 8 through 10; a response of "No" to this question (item 12) means that blood should NOT be collected for sending to the Genetics Repository and if already collected, should be destroyed by the Genetics Repository):*

(Yes 1) (No 2)

C. Administrative information

13. Study Physician PIN: ____ ____ ____

14. Study Physician signature:

_____

15. Clinical Coordinator PIN: ____ ____ ____

16. Clinical Coordinator signature:

_____

17. Date form reviewed:

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

Central Histology Review

Purpose: Record results of the NASH CRN Pathology Committee review of liver biopsy slides archived at the Histology Review Center.
When: Quarterly after the start of patient enrollment or more often as determined by the Pathology Committee.
By whom: Data Coordinating Center staff.
Instructions: Upon review of the liver biopsy slides by the NASH CRN Pathology Committee, the designated Data Coordinating Center staff member should complete the CR form. The CR form will be keyed by the Data Coordinating Center personnel.

A. Clinic, patient and visit identification

__ __ __ __ 1. Center ID

__ __ __ __ 2. Patient ID

__ __ __ 3. Patient code

__ __ / __ __ __ / __ __ 4. Date of central reading

__ __ __ __ 5. Visit code

c r 1 6. Form and revision

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

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

B. Slide sequence number

9. Sequence number for

__ __ . . . a. H & E stained slide

__ __ . . . b. Masson's trichrome stained slide

__ __ . . . c. Iron stained slide

__ __ . . . d. Other slide

_____ . . . . . Specify type of stain for other slide

C. Administrative information

__ __ __ 10. CC Initials

_____ 11. CC Signature

__ __ / __ __ __ / __ __ 12. Date form reviewed

__ 13. Tissue adequate: **0**=No ➜ Request original slides from submitting clinic; **1**=Yes

_____ 14. Followup with clinic (*Specify*):

_____ *Patient ID* **D. Histology**

_____ 15. Biopsy length (mm)

H & E stain

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

_____ . . . a. Grade: **0**=<5%; **1**=5-33%; **2**=34-66%; **3**=>66%

_____ . . . b. Location: **0**=Zone 3 (*central*); **1**=Zone 1 (*periportal*); **2**=Azonal; **3**=Panacinar

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

17. Inflammation

_____ . . . a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:
0=0; **1**=<2 under 20x mag; **2**=2-4 under 20 mag; **3**=>4 under 20 mag

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

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

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

18. Liver cell injury

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

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

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

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

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

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

Masson's trichrome stain

_____ 21. Fibrosis stage: **0**=None; **1a**=Mild, zone 3 perisinusoidal (*requires trichrome*);
1b=Moderate, zone 3, perisinusoidal (*does not require trichrome*); **1c**=Portal/periportal only;
2=Zone 3 and periportal, any combination; **3**=Bridging; **4**=Cirrhosis

22. Iron stain

_____ . . . a. Hepatocellular iron grade: **0**=Absent or barely discernible, 40x ➜ **GOTO item 22c**;
1=Barely discernable granules, 20x; **2**=Discrete granules resolved, 10x; **3**=Discrete granules resolved, 4x;
4=Masses visible by naked eye

_____ . . . b. Hepatocellular iron distribution: **0**=Periportal; **1**=Periportal and midzonal; **2**=Panacinar; **3**=Zone 3 or azonal

_____ . . . c. Nonhepatocellular iron grade: **0**=None ➜ **GOTO item 23**; **1**=Mild; **2**=More than mild

_____ . . . d. Nonhepatocellular iron distribution: **0**=Large vessel endothelium only; **1**=Portal/fibrosis bands only, but more than just in large vessel endothelium; **2**=Intraparenchymal only; **3**=Both portal and intraparenchymal

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

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

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

26. Features suggestive of steatohepatitis etiology for cryptogenic cirrhosis:

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

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

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

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

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

27. Other comments: _____

TONIC

DR - Death Report

Purpose: To record the report of a patient's death.
When: As soon as clinic is notified of a patient's death.
Administered by: Study Physician and Clinical Coordinator.
Instructions: Complete this form whenever the clinical center is informed of a patient's death. If the death is considered associated or possibly associated with participation in TONIC, complete a Serious Adverse Event (AN) form and follow the directions on Form AN for reporting a SAE in TONIC.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: n ____ ____ ____

6. Form & revision: d r 1

7. Study: TONIC_3

B. Death information

8. Date of death:

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

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

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

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

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

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

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

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

TONIC

DX - DEXA Scan for Body Fat

Purpose: To record DEXA scan measurements.
When: Visits s2 and f096.
Administered by: Clinical coordinator.
Instructions: A DEXA scan done in the year prior to starting screening for TONIC or during screening for TONIC may be used as the visit s2 DEXA scan. Transfer the DEXA scan measures from your institutional report to Section C. Attach a copy of the original DEXA report to this form.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: d x 1

7. Study: TONIC 3

B. DEXA scan information

8. Did the patient have a whole body dual energy x-ray absorptiometry (DEXA) scan:

(Yes 1) (No 2)

10.

9. Specify why DEXA scan was not performed

a. Patient is too heavy: (1)

b. Scanner is broken: (1)

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

_____
specify

14.

10. DEXA scanner used:

Hologic QDR 4500A (1)
Hologic QDR 4500W (2)
Hologic New Discovery Series 12.3 (3)
Hologic Delphi QDR Series (4)
Hologic Delphi W (5)
Lunar Prodigy (6)
Other *(specify)* (7)

_____
specify make & model

C. DEXA results summary

11. Date of DEXA scan:

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

12. Trunk % fat *(if your scanner reports both tissue % fat and region % fat, record region % fat on this report):*

____ ____ • ____ ____
%

13. Total % fat *(if your scanner reports both tissue % fat and region % fat, record region % fat on this report):*

____ ____ • ____ ____
%

C. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

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

TONIC

EC - Eligibility Checklist

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

When: Visit rz.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: This form may be initiated at any time. If the patient proceeds to randomization, it must be reviewed on the day of randomization. Patients of childbearing potential must complete the randomization day pregnancy test at the clinic on the day of randomization. Patients who are not of childbearing potential may complete the randomization day visit over the telephone. If this is the case, these requirements must be followed:

(1) If your consent statement has an area for affirmation of consent prior to randomization, the patient should have signed the affirmation at his/her last screening visit.

(2) The clinical coordinator must confirm with the patient by telephone on the day of randomization, that the patient feels well and continues to consent to randomization.

(3) The assigned study medication must be mailed to the patient on the day of randomization for delivery the next day.

(4) The patient should be instructed to start the medications as soon as possible after receipt.

If Elig is checked for any item, complete the entire form, but note that the patient may not continue in the TONIC trial. If an item has not been assessed because the patient is ineligible, write ''m'' (missing) next to that item. This form should be completed for each patient for whom form RG was completed

A. Center, patient, visit, and study identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: r z ____ ____

6. Form & revision: e c 1

7. Study: TONIC 3

B. Alcohol use exclusion

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

Yes (1) → Elig No (2)

9. In the judgment of the Study Physician and/or Clinical Coordinator, can the patient (or the patient's parent/guardian) reliably quantify the child's *(past and current)* alcohol intake:

Yes (1) No (2) → Elig

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

Yes (1) No (2) → Elig

C. Cirrhosis exclusion

11. Clinical cirrhosis evaluation

a. Does the patient have varices or ascites and does the Study Physician judge that the patient has cirrhosis:

Yes (1) No (2) Elig

b. In the Study Physician's judgment, does the patient have cirrhosis *(INR > 1.3, albumin < 3.0 g/dL, or conjugated bilirubin > 2 mg/dL may indicate cirrhosis):*

Yes (1) No (2) Elig

D. Other chronic liver disease exclusions

12. Evidence of autoimmune liver disease

a. Does the patient have ongoing autoimmune liver disease defined by the presence of anti-nuclear antibody (ANA) of greater than 1:80 and liver histology consistent with autoimmune liver disease:

Yes (1) No (2) Elig

b. In the Study Physician's judgment, does the patient have a history of autoimmune hepatitis:

Yes (1) No (2) Elig

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

Yes (1) No (2) Elig

14. Does the patient have alpha-1 antitrypsin (A1AT) deficiency confirmed by A1AT level less than normal *(physician judgment):*

Yes (1) No (2) Elig

15. Does the patient have an iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:

Yes (1) No (2) Elig

16. Do any of the patient's assessments show evidence of other chronic liver disease

a. Drug induced liver disease as defined on the basis of typical exposure and history:

Yes (1) No (2) Elig

b. Known bile duct obstruction:

Yes (1) No (2) Elig

c. Any other type of liver disease other than NAFLD that warrants exclusion from the trial:

Yes (1) No (2) Elig

E. Other medical exclusions

17. History of metabolic acidosis:

Yes (1) No (2) Elig

18. History of renal dysfunction:

Yes (1) No (2) Elig

19. History of coagulopathy:

Yes (1) No (2) Elig

20. History of diabetes mellitus:

Yes (1) No (2) Elig

21. History of bariatric surgery *(jejunoileal bypass or gastric weight loss surgery):*

Yes (1) No (2) Elig

22. History of hepato-biliary surgery:

Yes (1) No (2) → Elig

23. Inability to safely undergo liver biopsy:

Yes (1) No (2) → Elig

24. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the 2 years prior to screening:

Yes (1) No (2) → Elig

25. Use of antidiabetic drugs in the 3 months prior to randomization:

Yes (1) No (2) → Elig

26. Use of antiNAFLD drugs in the 3 months prior to randomization:

Yes (1) No (2) → Elig

27. Use of antiobesity drugs in the 3 months prior to randomization:

Yes (1) No (2) → Elig

28. Use of Vitamin E at a dose greater than 100 IU/day in the 3 months prior to randomization:

Yes (1) No (2) → Elig

29. Known active, serious medical disease with a likely life-expectancy less than 5 years:

Yes (1) No (2) → Elig

30. Known active substance abuse, such as alcohol or inhaled or injection drugs in the year prior to screening:

Yes (1) No (2) → Elig

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

Yes (1) No (2) → Elig

F. Birth control exclusion

32. In the judgment of the Study Physician and/or Clinical Coordinator, is the patient willing to use effective birth control methods to avoid pregnancy during the 96 weeks of treatment:

Male or not of childbearing potential (0)
Yes (1)
No (2) → Elig

G. Check on ability to swallow study medication

33. In your judgment (Study Physician/Clinical Coordinator), is the patient able to swallow the TONIC study medications *(if you are unsure, you may ask the patient to swallow a capsule from the sample bottle of placebo metformin sent by the DCC prior to the start of TONIC):*

Yes (1) No (2) → Elig

H. Eligibility check on day of randomization

(Do in person if patient is of childbearing potential; otherwise, these checks may be done over the telephone with the patient on the day of randomization.)

34. Was an ineligibility condition checked or an eligibility not ascertained in items 8-33:

Yes (1) No (*2)

43. ____

**Key visits s1 and s2 forms RG, AD, BC, BD, BG, BP, CG, DX, HF, LP, LR, LS, LU, MA, MR (if available), PE, PQ/PR, PY/PW, SD. Run the Randomization Task on your clinic data system.*

35. Were any stops or ineligible conditions other than ''missing form EC'' identified by the Randomization Task:

Yes (1) → **43.**

No (2)

Task not run because patient is known to be ineligible (3) → **43.**

36. Does the patient feel well today:

Yes (1) — No (*2) → STOP

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

37. Is the patient male:

Yes (1) → **41.** — No (2)

38. Is the patient of childbearing potential:

Yes (*1) — No (2) → **40.**

**Administer pregnancy test.*

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

Yes (*1) → Elig — No (2)

**Go to item 43.*

40. Is the patient currently breast feeding:

Yes (*1) → Elig — No (2)

**Go to item 43.*

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

Yes (*1) → Elig — No (2)

**If Yes, specify reason and then go to item 43:*

_____
specify reason

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

Yes (*1) → **44.** — No (†2) → Elig

**Go to item 44 and complete this form. Then key this form and run the Randomization Task on your clinic data system to randomize the patient.*

†Complete items 43-48 and key the form. The form must be keyed to document the reasons for ineligibility for TONIC.

I. Reasons for ineligibility for ineligible patients

Note: Complete this section for ineligible patients only.

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

a. Reason covered in items 8-42: (1)

b. Biopsy out of window and patient chose not to repeat: (1)

c. Biopsy inadequate for scoring and patient chose not to repeat: (1)

d. Local pathologist did not find steatosis: (1)

e. Creatinine ≥ 1.5 mg/dL for males or creatinine ≥ 1.4 mg/dL for females: (1)

f. Positive for hepatitis B: (1)

g. Positive for hepatitis C: (1)

h. ALT< 60 U/L: (1)

i. ALT > 400 U/L: (1)

j. Fasting serum glucose ≥ 126 mg/dL or 2 hour serum glucose ≥ 200 mg/dL: (1)

k. Known intolerance to metformin: (1)

l. Known intolerance to vitamin E: (1)

m. Liver transplant: (1)

n. Currently being evaluated for bariatric surgery: (1)

o. TPN in the past 3 years prior to screening: (1)

p. Inability to swallow study medication: (1)

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

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

_____
specify

J. Administrative information

44. Study Physician PIN: ____ ____ ____

45. Study Physician signature:

_____

46. Clinical Coordinator PIN: ____ ____ ____

47. Clinical Coordinator signature:

_____

48. Date form reviewed
(Note re: patient proceeding to randomization: this form must be reviewed on the day of randomization; if it was keyed prior to the randomization day, update it and re-review it on the day of randomization and key the revised date of review.):

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

(NOTE: If patient was not present in the clinic to receive the assigned medication, send the medication to the patient by overnight delivery service.)

TONIC

HI - Followup Medical History

Purpose: To record followup medical history information about the patient.
When: Visits f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.
Administered by: Clinical Coordinator, reviewed by Study Physician.
Respondent: Patient.
Instructions: Collect information by interview or chart review.

A. Center, visit, and patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: h i 1

7. Study: TONIC 3

B. Interval identification

8. Date of last Followup Medical History form *(if this is visit f004 then date of s1):*

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

9. Visit code of last Followup Medical History form *(if this is visit f004 then s1):*

____ ____ ____ ____

C. NAFLD evaluation

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

(* Yes 1) (No 2)

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

D. Alcohol consumption (AUDIT-C) since the last visit *(interview with patient)*

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

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

14. ____

12. Since the last visit, how many drinks containing alcohol did you have on a typical day when you are drinking:

1 or 2	(0)
3 or 4	(1)
5 or 6	(2)
7 to 9	(3)
10 or more	(4)

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

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

E. Tobacco cigarette smoking *(interview with patient)*

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

(Yes 1) (No 2)

17. ⌊

15. On average, how many days per week have you smoked cigarettes: ____ # days

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

____ ____ ____ # cigarettes per day

F. Medical history

17. Since the last visit, has the patient been diagnosed with or treated for any of the following *(check all that apply; source of information can be interview and/or chart review)*

a. Diabetes type 1: (1)
b. Diabetes type 2: (1)
c. Gestational diabetes *(diabetes of pregnancy):* (1)
d. Hepatitis B: (1)
e. Hepatitis C: (1)
f. Autoimmune hepatitis: (1)
g. Autoimmune cholestatic liver disorder (PBC or PSC): (1)
h. Wilson's disease: (1)
i. Alpha-1-antitrypsin (A1AT) deficiency: (1)
j. Hemochromatosis or iron overload: (1)
k. Drug induced liver disease: (1)
l. Gilbert's syndrome: (1)
m. Esophageal or gastric varices on endoscopy: (1)
n. Bleeding from varices: (1)
o. Other gastrointestinal bleeding: (1)
p. Biliary diversion: (1)
q. Metabolic acidosis: (1)
r. Ascites: (1)
s. Edema: (1)
t. Hepatic encephalopathy: (1)
u. Portal hypertension: (1)
v. Hepatorenal syndrome: (1)
w. Hepatopulmonary syndrome: (1)
x. Short bowel syndrome: (1)
y. Hemophilia *(bleeding disorder):* (1)
z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: (1)
aa. Endocrine disease *(hormonal abnormality):* (1)
ab. Hepatocellular carcinoma: (1)
ac. Other malignancy *(cancer):* (1)
ad. Human immunodeficiency virus (HIV): (1)
ae. Peripheral neuropathy: (1)
af. Seizure disorder or epilepsy: (1)
ag. Drug allergies: (1)
ah. Hypothyroidism: (1)
ai. Hypertension: (1)
aj. Cerebrovascular disease: (1)
ak. Dysbetalipoproteinemia: (1)
al. Hyperlipidemia *(high cholesterol, high triglycerides):* (1)
am. Pancreatitis: (1)
an. Cholelithiasis: (1)
ao. Coronary artery disease: (1)
ap. Congestive heart failure: (1)
aq. Elevated uric acid such as gout: (1)
ar. Kidney disease: (1)
as. Polycystic ovary syndrome: (1)
at. Sleep apnea *(not breathing during sleep):* (1)
au. Dermatologic disorders: (1)
av. Myopathy: (1)
aw. Myositis: (1)

ax. Major depression: (1)

ay. Schizophrenia: (1)

az. Bipolar disorder: (1)

ba. Obsessive compulsive disorder: (1)

bb. Severe anxiety or personality disorder: (1)

bc. Substance abuse: (1)

bd. None of the above: (1)

18. Since the last visit, has the patient had bariatric surgery for any of the following *(check all that apply)*

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

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

c. Biliopancreatic diversion: (1)

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

_____

e. None of the above: (1)

19. Since the last visit, has the patient received an organ, limb, or bone marrow transplant:

(Yes 1) (No 2)

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

(Yes 1) (No 2)

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

(Yes 1) (No 2)

22. ____

If Yes, specify reason:

_____
specify

22. Since the last visit, has the patient had any serious health problem not already reported:

(Yes 1) (No 2)

23. ____

If Yes, specify:

_____
specify

G. Medication use

23. Since the last visit, has the patient used any antidiabetic medications *(check all that apply):*

a. Acarbose (Precose): (1)

b. Acetohexamide (Dymelor): (1)

c. Chlorpropamide (Diabinese): (1)

d. Glimepiride (Amaryl): (1)

e. Glipizide (Glucotrol, Glucatrol XL): (1)

f. Glyburide (Micronase, DiaBeta, Glynase): (1)

g. Insulin: (1)

h. Metformin (Glucophage, Glucophage XR) *(do not include TONIC study medication):* (1)

i. Miglitol (Glycet): (1)

j. Nateglinide (Starlix): (1)

k. Pioglitazone (Actos): (1)

l. Repaglinide (Prandin): (1)

m. Rosiglitazone (Avandia): (1)

n. Tolazamide (Tolinase): (1)

o. Tolbutamide (Orinase): (1)

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

_____

q. None of the above: (1)

24. Since the last visit, has the patient taken any lipid lowering medications *(check all that apply):*

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

_____

m. None of the above: (1)

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

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

_____

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

_____

j. None of the above: (1)

26. Since the last visit, has the patient taken any pain relieving, non-steroidal anti-inflammatory, or aspirin containing medications *(check all that apply):*

a. Acetaminophen (Tylenol): (1)
b. Aspirin - 325 mg: (1)
c. Celecoxib (Celebrex): (1)
d. Ibuprofen (Advil, Motrin): (1)
e. Indomethacin (Indocin): (1)
f. Naproxen (Aleve, Naprosyn): (1)
g. Valdecoxib (Bextra): (1)
h. Other, *(specify):* (1)

_____

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

_____

j. None of the above: (1)

27. Since the last visit, has the patient taken any histamine H2 receptor antagonists or other gastrointestinal medications *(check all that apply):*

a. Cimetidine (Tagamet): (1)
b. Esomeprazole magnesium (Nexium): (1)
c. Famotidine (Pepcid): (1)
d. Lansoprazole (Prevacid): (1)
e. Nizatidine (Axid): (1)
f. Omeprazole (Prilosec): (1)
g. Ranitidine (Zantac): (1)
h. Ranitidine bismuth citrate (Tritec): (1)
i. Antacids, *(specify):* (1)

_____

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

_____

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

_____

l. None of the above: (1)

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

a. Betamethasone sodium (Celestone): (1)
b. Cortisol: (1)
c. Cortisone: (1)
d. Dexamethasone (Decadron): (1)
e. Hydrocortisone (Hydrocortone): (1)
f. Methylprednisolone (Solu-Medrol): (1)
g. Prednisolone (Prelone): (1)
h. Prednisone: (1)
i. Triamcinolone (Acetocot, Amcort, Aristocort, Kenacort): (1)
j. Other, *(specify):* (1)

_____

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

_____

l. None of the above: (1)

29. Since the last visit, has the patient taken any anabolic steroids or tamoxifen *(check all that apply):*

a. Boldenone undecylenate (Equipoise): (1)
b. Fluoxymesterone (Android-F, Halotestin): (1)
c. Methandrostenolone (Dianabol): (1)
d. Methyltestosterone (Android): (1)
e. Nandrolone (Deca-Durabolin, Hybolin Decanoate, Kabolin): (1)
f. Oxandrolone (Oxandrin): (1)
g. Oxymetholone (Anadrol): (1)
h. Stanzolol (Winstrol): (1)
i. Tamoxifen (Nolvadex): (1)
j. Testosterone (Depo Testosterone): (1)
k. Other, *(specify):* (1)

_____

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

_____

m. None of the above: (1)

30. Since the last visit, has the patient taken any allergy or asthma medications *(check all that apply):*

a. Albuterol: (1)
b. Beclomethasone dipropionate (Beclovent, Vanceril): (1)
c. Budesonide (Pulmicort, Rhinocort): (1)
d. Fluticasone propionate (Flonase, Flovent): (1)
e. Loratadine (Claritin): (1)
f. Mometasone furoate (Nasonex): (1)
g. Triamcinolone acetonide (Azmacort, Nasacort): (1)
h. Other, *(specify):* (1)

_____

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

_____

j. None of the above: (1)

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

Yes (1) No (2)

32. Since the last visit, has the patient taken vitamins other than multivitamins *(do not include TONIC study medication):*

Yes (1) No (2)

35. ____

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

a. Vitamin B (any type): (1)
b. Vitamin C: (1)
c. Vitamin D: (1)
d. Vitamin E (alpha-tocopherol): (1)
e. Other, *(specify):* (1)

_____

34. Is the patient currently taking vitamin E at a dose greater than 100 IU/day *(do not include TONIC study medication):*

Yes (*1) No (2)

**Remind patient not to take vitamin E supplements at doses greater than 100 IU/day during TONIC.*

35. Since the last visit, has the patient taken any supplements *(check all that apply):*

a. Alpha-lipoic acid: (1)
b. Beta-carotene: (1)
c. Betaine (Cystadane): (1)
d. Calcium (any form): (1)
e. Carnitine (any form): (1)
f. Chondroitin (any form): (1)
g. Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
h. Cod liver oil: (1)
i. Coenzyme Q: (1)
j. Dichloroacetate: (1)
k. Echinacea: (1)
l. Fish oil (any form): (1)
m. Flax seed oil: (1)
n. Garlic: (1)
o. Ginkgo biloba: (1)
p. Glucosamine (any form): (1)
q. Lecithin: (1)
r. Magnesium: (1)
s. Milk thistle: (1)
t. N-acetyl-cysteine: (1)
u. Potassium (any form): (1)
v. Probiotics (any form): (1)
w. S-adenylmethionine (SAM-e): (1)
x. Saw palmetto: (1)
y. Selenium: (1)
z. St. John's Wort: (1)
aa. Taurine: (1)
ab. Zinc picolinate: (1)
ac. Other, *(specify):* (1)

_____

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

_____

ae. None of the above: (1)

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

a. Acetylsalicylic acid (ASA): (1)
b. Aspirin - 325 mg: (1)
c. Demeclocycline (Declomycin): (1)
d. Divalproex (Depakote): (1)
e. Doxycycline (Monodox): (1)
f. Isotretinoin (Accutane): (1)
g. Levonorgestrel (Norplant): (1)
h. Levothyroxine (Levoxyl, Synthroid): (1)
i. Liothyronine (Cytomel): (1)
j. Minocycline (Dynacin, Minocin): (1)
k. Oral contraceptives: (1)
l. Oxytetracycline (Terramycin): (1)
m. Penicillamine (Cuprimine, Depen): (1)
n. Tetracycline (Achromycin): (1)
o. Trientine hydrochloride (Syprine): (1)
p. Ursodeoxycholic acid (Actigall, Urso, Ursodiol): (1)
q. Valproate sodium (Depacon): (1)
r. Valproic acid (Depakene): (1)
s. Other, *(specify):* (1)

_____

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

_____

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

_____

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

_____

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

_____

x. None of the above: (1)

H. Administrative information

37. Study Physician PIN: ____ ____ ____

38. Study Physician signature:

_____

39. Clinical Coordinator PIN: ____ ____ ____

40. Clinical Coordinator signature:

_____

41. Date form reviewed:

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

TONIC

LP – Symptoms of Liver Disease (Children)

Purpose: To obtain the patient's view of his/her liver disease symptoms.
When: Visits s2, f048, f096, and f120.
Administered by: Self-administered (age 13-17), interviewer administered (age 8-12). Clinical Coordinator must be available to answer questions and review for completeness.
Respondent: Patient, age 8 through 17. Patient age 13 or older should complete the form without help from family. Clinical Coordinator/parent should assist patient age 8-12.
Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-4. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in the completion of the form, and then should complete pages 2-4. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should then complete section B below.

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit:

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

5. Visit code: _____ _____ _____ _____

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

7. Study: TONIC 3

B. Administrative information

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

8. How was the questionnaire completed:

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

9. Who was the respondent *(check all that apply)*:

a. Patient: (1)
b. Patient's mother or female guardian: (1)
c. Patient's father or male guardian: (1)
d. Other *(specify)*: (1)

_____
specify

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

_____

11. Date form reviewed:

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

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

Symptoms of Liver Disease

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

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

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

Circle one for each symptom

Degree of bother

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

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

Circle one for each symptom

Degree of bother

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

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

Circle one

I feel normal and am not tired **(If this is how you feel, please circle "1" and go to item number 17 – Thank you!)** 1
I feel tired some of the time, but can do what I want to do without trouble 2
I feel tired, and do what I want but with trouble 3
I feel tired and it keeps me from doing what I want to do 4

14. How often are you bothered by being tired *(choose only one)*:

All day, every day 1
Part of the day, every day 2
At least part of several days a week 3
At least part of one day a week 4
Not as much as above 5

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

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

16. Do you feel more tired the day after you exercise or have a lot of activity:

Yes 1
No 2

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

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

Very good 1
Good 2
Fair 3
Poor 4
Awful 5

18. Today's date:

_____

Thank you for completing this questionnaire.

TONIC

LR - Laboratory Results - Tests Done at Visit s1 and During Followup

Purpose: To record archival and current laboratory test results for tests done during both screening and followup.
When: Visits s1, f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.
Administered by: Study Physician and Clinical Coordinator.
Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If (FNE) is checked in item 63, the patient is not eligible for TONIC and the form should not be keyed. Attach copies of the laboratory reports to this form.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: l r 1

7. Study: TONIC 3

B. Initial screening ALT

8. Is this visit s1:

( ) Yes (1) ( ) No (2) → **11.**

9. Date of blood draw for ALT
(Date must be within 12 months of randomization and at least 30 days apart from the ALT done at the clinic for visit s2):

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

10. Alanine aminotransferase (ALT) *(if ALT ≤ 60 U/L, patient is ineligible; also, patient is ineligible if the ALT done closest in time to randomization is > 400 U/L):*

____ ____ ____
U/L

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

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

C. Hematology

Required at visits s1, f024, f048, f072, f096, and f120.

11. Is hematology testing required at this visit:

( ) Yes (1) ( ) No (2) → **17.**

12. Date of blood draw for hematology:

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

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

13. Hemoglobin: ____ ____ • ____
g/dL

14. Hematocrit: ____ ____ • ____
%

15. White blood cell count (WBC):

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

16. Platelet count:

____ ____ ____, ____ ____ ____
cells/ µL

D. Metabolic panel

Required at all visits using the LR form (s1, f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120).

17. Date of blood draw for metabolic panel:

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

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

18. Sodium: ____ ____ ____ mEq/L

19. Potassium: ____ ____ • ____ mEq/L

20. Chloride: ____ ____ ____ mEq/L

21. Bicarbonate: ____ ____ • ____ mEq/L

22. Calcium: ____ ____ • ____ mg/dL

23. Phosphate: ____ ____ • ____ mg/dL

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

25. Creatinine *(if serum creatinine ≥ 1.5 (1.4) mg/dL and patient is male (female), patient is ineligible):*

____ ____ • ____ mg/dL

26. Uric acid: ____ ____ • ____ mg/dL

27. Albumin: ____ • ____ g/dL

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

E. Fasting lipid profile

Required at visits s1, f024, f048, f072, f096, and f120.

Fasting is defined as nothing by mouth except water for greater than or equal to 12 hours prior to blood draw.

29. Is fasting lipid profile required at this visit:

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

31. ⌊

30. Date of blood draw for fasting lipid profile:

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

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

a. Triglycerides: ____ ____ ____ mg/dL

b. Total cholesterol: ____ ____ ____ mg/dL

c. HDL cholesterol level: ____ ____ ____ mg/dL

d. LDL cholesterol level: ____ ____ ____ mg/dL

F. Fasting glucose

Required at visits s1, f024, and f072. Also required at visits f048, f096, and f120 if the patient is diabetic.

Fasting is defined as nothing by mouth except water for at least 12 hours prior to blood draw.

31. Is fasting glucose required at this visit:

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

34. ⌊

32. Date of blood draw for fasting glucose level:

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

Date must be within the required time window; within 3 months of screening or in the time window for the followup visit (check the patient's TONIC visit time window guide).

33. Serum glucose *(if fasting glucose 126 mg/dL or greater, patient is ineligible):*

____ ____ ____
mg/dL

G. Hepatic panel

Required at visits f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.

34. Is hepatic panel required at this visit:

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

41.

35. Date of blood draw for hepatic panel:

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

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

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

37. Bilirubin (conjugated or direct):

____ ____ • ____
mg/dL

38. Aspartate aminotransferase (AST)

____ ____ ____
U/L

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

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

39. Alanine aminotransferase (ALT)

____ ____ ____
U/L

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

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

40. Alkaline phosphatase ____ ____ ____
U/L

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

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

H. Vitamin B_{12}

Required at visits f024, f048, f072, f096, and f120.

41. Is vitamin B_{12} required at this visit:

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

44.

42. Date of blood draw for vitamin B_{12}:

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

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

43. Vitamin B_{12} (cobalamin) *(if provided in pmol/L, multiply by 1.35 to convert to pg/ml):*

____ ____ ____ ____ • ____
pg/mL

I. Prothrombin time, GGT, and HbA1c

Required at visits f048, f096, and f120.

44. Are the prothrombin time, GGT, and HbA1c tests required a this visit:

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

50.

45. Date of blood draw for prothrombin time, GGT, and HbA1c:

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

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

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

47. International normalized ratio (INR):

____ • ____

48. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

49. HbA1c: ____ ____ • ____
%

J. Oral glucose tolerance test

Required at visits f048, f096, and f120.

The oral glucose tolerance test will be performed. in the morning after a 12-hour overnight fasting. Baseline blood sample will be obtained for measurements of serum glucose, insulin, and C peptide. Blood sample will be obtained after 2 hours (120 minutes) for the measurement of serum glucose and insulin after oral administration of flavored glucose solution in a dose of 2 g/kg (75 g maximum).

50. Is oral glucose tolerance test (OGTT) required at this visit:

Yes (1)
No (2)
54.
No, patient is diabetic (3)
54.

51. Date of blood draw for OGTT:

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

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

52. OGTT results at baseline

a. Serum glucose: ____ ____ ____ mg/dL

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

c. Serum C peptide: ____ ____ ____ • ____ ng/mL

53. OGTT results at 2 hours

a. Serum glucose: ____ ____ ____ mg/dL

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

K. Free fatty acid, leptin, and C-reactive protein

Required at f048, f096, and f120.

54. Are free fatty acid, leptin, and C-reactive protein required at this visit:

Yes (1) No (2)
59.

55. Date of blood draw for free fatty acid, leptin and C-reactive protein (all serum):

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

Date must be in the time window for the followup visit (check the patient's TONIC visit time window guide).

56. Free fatty acid: ____ ____ ____ ____ µmol/L

57. Leptin: ____ ____ • ____ ng/mL

58. C-reactive protein *(if result is reported as normal but below your lab's detectable level, enter the cutoff for your lab's detectable level):*

____ ____ ____ • ____ mg/dL

If units reported are mg/L, divide by 10 to convert to mg/dL.

L. Pregnancy test

Required at all study visits if applicable.

59. Is pregnancy test applicable:

Yes (1) No (2)
62.

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

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

Date must be the same day as date of visit.

61. Pregnancy test results *(if pregnancy test is positive at s1, patient is ineligible):*

Positive (1)
Negative (2)

M. Eligibility check

62. Is this the s1 visit:

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

If No (2) → **64.**

63. Was the patient found to be ineligible based on ALT (item 10), creatinine (item 25), fasting serum glucose (item 33), or pregnancy test (item 61):

( ) Yes (1) → Elig (5) ( ) No (2)

N. Administrative information

64. Study Physician PIN: ____ ____ ____

65. Study Physician signature:

_____

66. Clinical Coordinator PIN: ____ ____ ____

67. Clinical Coordinator signature:

_____

68. Date form reviewed:

____ ____–____ ____ ____–____ ____

day mon year

TONIC

LS - Laboratory Results
Tests Done Only During Screening

Purpose: To record archival and current results of laboratory tests done only at screening.
When: Visit s1.
Administered by: Study Physician and Clinical Coordinator.
Instructions: Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. If Elig is checked for any item the patient is not eligible for the TONIC trial. If C is checked for an item, use caution. If the Study Physician agrees with the diagnosis, the patient is ineligible for TONIC.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: s 1 ____ ____

6. Form & revision: 1 s 1

7. Study: TONIC 3

B. Screening etiologic tests

8. Date of blood draw for serological assays to exclude viral causes of chronic liver disease:

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

Repeat if date is greater than 1 year prior to screening.

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

b. Hepatitis B core total antibody (anti-HBc) *(if total anti-HBc is not available, record results from IgG test):*
Positive (1)
Negative (2)
Not available (3)

c. Hepatitis B surface antibody (anti-HBs):
Positive (1)
Negative (2)
Not available (3)

d. Hepatitis C antibody (anti-HCV) *(indicate result as negative if EIA is positive but RIBA is negative):*
Positive (1) Elig
Negative (2)

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

C. Autoantibody studies

9. Date of blood draw for autoantibody tests:

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

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

10. Antinuclear antibody (ANA):

Positive (* 1)
Negative (2)

12.

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

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

11. Is ANA titration greater than 1:80

Yes (* 1) No (2)

C

** Check Liver Biopsy Histology Findings Form for autoimmune liver disease.*

12. Antismooth muscle antibody (ASMA):

Positive (* 1)
Negative (2)

13.

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

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

13. Antimitochondrial antibody (AMA):

Positive (* 1)
Negative (2)

15.

Not available (3)

15.

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

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

14. Is AMA titration greater than 1:80

Yes (* 1) No (2)

C

** Check Liver Biopsy Histology Findings Form for primary biliary cirrhosis.*

D. Ceruloplasmin

15. Date of blood draw for ceruloplasmin:

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

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

16. Ceruloplasmin ____ ____ • ____ ____
mg/dL

a. Lower limit of normal: ____ ____ • ____ ____
mg/dL

b. Is ceruloplasmin below the lower limit of normal:

Yes (* 1) No (2)

C

** Check Liver Biopsy Histology Findings Form for Wilson's Disease.*

E. Alpha-1 antitrypsin

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

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

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

18. Alpha-1 antitrypsin (A1AT)

____ ____ ____
mg/dL

a. Lower limit of normal: ____ ____ ____
mg/dL

b. A1AT deficiency (physician judgment):

Yes (1) No (2)

Elig

F. Iron

19. Date of blood draw for hemochromatosis screening:

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

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

a. Iron: ____ ____ ____ µg/dL

b. Total Iron Binding Capacity: ____ ____ ____ µg/dL

c. Ferritin: ____ ____ ____ ____ ng/mL

20. Is hepatic iron index available:

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

22.

21. Hepatic iron index: ____ • ____ µmol/g/year

G. Administrative information

22. Study Physician PIN: ____ ____ ____

23. Study Physician signature:

_____

24. Clinic Coordinator PIN: ____ ____ ____

25. Clinic Coordinator signature:

_____

26. Date form reviewed:

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

TONIC

LU - Laboratory Results - Tests Required at Visit s2

Purpose: To record archival and current laboratory test results for tests required at visit s2.

When: Visit s2.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review except for hepatic panel which must be done at the TONIC clinical center on or after the date when screening started. Note that the ALT recorded for visit s1 and this hepatic panel (visit s2) must have been done at least 30 days apart. The hepatic panel done at visit s2 may pre-date the ALT recorded on the visit s1 LR form so long as the visit s2 hepatic panel is done on or after the date screening started. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If ⊘ is checked in any item, the patient is not eligible for TONIC and the form should not be keyed. Attach copies of the laboratory reports to this form.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: l u 1

7. Study: TONIC 3

B. Hepatic panel

This hepatic panel must be done at TONIC clinical center on or after the date when screening started, and the ALT recorded in the s1 LR form and this hepatic panel (visit s2) must be at least 30 days apart, but this hepatic panel may pre-date the ALT recorded on the visit s1 LR form.

8. Date of blood draw for hepatic panel:

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

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

10. Bilirubin (conjugated or direct):

____ • ____
mg/dL

11. Aspartate aminotransferase (AST)

____ ____ ____
U/L

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

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

12. Alanine aminotransferase (ALT) *(if ALT ≤ 60 U/L, patient is ineligible; patient is also ineligible if the ALT done closest in time to randomization is > 400 U/L)*

____ ____ ____
U/L

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

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

13. Alkaline phosphatase ____ ____ ____
U/L

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

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

C. Vitamin B_{12}, free fatty acid, leptin, and C-reactive protein

14. Date of blood draw for vitamin B_{12}, free fatty acid, leptin, and C-reactive protein (all on serum):

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

Date must be within 3 months of screening.

15. Vitamin B_{12} *(if provided in pmol/L, multiply by 1.35 to convert to pg/ml):*

____ ____ ____ ____ • ____
pg/mL

16. Free fatty acid: ____ ____ ____ ____
µmol/L

17. Leptin: ____ ____ • ____
ng/mL

18. C-reactive protein *(if result is reported as normal but below your lab's detectable level, enter the cutoff for your lab's detectable level):*

____ ____ ____ • ____
mg/dL

If units reported are mg/L, divide by 10 to convert to mg/dL.

D. Prothrombin time, GGT and HbA1c

19. Date of blood draw for prothrombin time, GGT, and HbA1c:

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

Date must be within 3 months of screening.

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

21. International normalized ratio (INR):

____ • ____

22. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

23. HbA1c: ____ ____ • ____
%

E. Oral glucose tolerance test

The oral glucose tolerance test will be performed in the morning after a 12-hour overnight fast. Baseline blood sample will be obtained for measurements of serum glucose, insulin, and C peptide. Blood samples will be obtained at 2 hours (120 minutes) for the measurement of serum glucose and insulin after oral administration of flavored glucose solution in a dose of 2 g/kg (75 g maximum).

24. Date of blood draw for OGTT:

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

Date must be within 3 months of screening.

25. OGTT results at baseline

a. Serum glucose *(if fasting glucose 126 mg/dL or greater, patient is ineligible):*

____ ____ ____
mg/dL

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

c. Serum C peptide: ____ ____ • ____
ng/mL

26. OGTT results at 2 hours *(if 2-hour glucose ≥ 200 mg/dL, patient is ineligible)*

a. Serum glucose: ____ ____ ____
mg/dL

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

F. Pregnancy test

27. Is pregnancy test applicable:

Yes (1) No (2)

30.

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

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

Date must be the same day as date of visit.

29. Pregnancy test results *(if pregnancy test is positive at s1 or s2, patient is ineligible):*

Positive (1)
Negative (2)

G. Eligibility check

30. Was the patient found to be ineligible based on ALT (item 12), fasting serum glucose (item 25a), 2-hour glucose (item 26a), or pregnancy test (item 29):

Yes (1) → Elig

No (2)

H. Administrative information

31. Study Physician PIN: ____ ____ ____

32. Study Physician signature:

_____

33. Clinical Coordinator PIN: ____ ____ ____

34. Clinical Coordinator signature:

_____

35. Date form reviewed:

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

Keyed: ( )

TONIC

MA - Modifiable Activity Questionnaire

Purpose: To obtain the patient's physical activity.
When: Visits s2, f048, f096, and f120.
Administered by: Interview administered (8-12 yrs) or self-administered (13-17 yrs). Parents may assist with completion, if needed. Clinical Coordinator must be available at visits to answer questions and to review completed forms.
Respondent: Patient.
Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-3. The patient should meet with the interviewer, be trained in completion of the form, and then should complete pages 2-3. If needed, the Clinical Coordinator may administer the interview to the patient. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator should complete section B below.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

____ ____ - ____ ____ ____ - ____ ____
day month year

5. Visit code: ____ ____ ____ ____

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

7. Study: TONIC 3

B. Administrative information

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

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

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

10. Clinical Coordinator
a. PIN: ____ ____ ____

b. Signature: _____

11. Date form reviewed:

____ ____ - ____ ____ ____ - ____ ____
day month year

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

Modifiable Activity Questionnaire

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

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

Circle one

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

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

Circle one

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

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

Circle one

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

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

Circle one

None 1
1 activity 2
2 activities 3
3 activities 4
4 or more activities 5

What activities did you compete in?

_____

_____

_____

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

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

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

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

List each activity that you checked above in the "Activity" box below.
Check the months you did each activity and then estimate the amount of time spent in each activity.

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

17. Today's date: ________________________________

TONIC

PE - Physical Examination

Purpose: Record detailed physical exam findings.

When: Visits s1, f048, f096, and f120.

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

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

One of the eligibility criteria for TONIC is the ability to swallow TONIC study medications. If you are unsure about the patient's ability to swallow the study medication, you may ask the patient to swallow a capsule from the bottle of placebo metformin sent to the clinical center by the DCC before the start of TONIC. The physical examination might be a logical time to ask the patient about this/ask for a demonstration. If the patient is unable to swallow the placebo and is ineligible (item 44=2), the PE form should not be keyed.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: p e 1

7. Study: TONIC 3

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement:

____ ____ ____ • ____

b. Weight, 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

10. Waist *(standing, at midpoint between highest point of iliac crest and lowest part of costal margin; repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. Circumference, 1st measurement:

____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
waist circumference

c. Units:

Inches (1)
Centimeters (2)

11. Hip *(standing, at fullest part of the hips; repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. Circumference, 1st measurement:

___ ___ ___ • ___
hip circumference

b. Circumference, 2nd measurement:

___ ___ ___ • ___
hip circumference

c. Units:

Inches (1)
Centimeters (2)

12. Triceps *(right arm, with elbow extended and arm relaxed; repeat skin fold measurements until you have two within 10 mm of each other; repeat mid-upper arm circumference until you have two within 1.5 in (3.8 cm) of each other)*

a. Skin fold, 1st measurement:

___ ___ ___ • ___
mm

b. Skin fold, 2nd measurement:

___ ___ ___ • ___
mm

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

___ ___ • ___
arm circumference

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

___ ___ • ___
arm circumference

e. Units for arm circumference:

Inches (1)
Centimeters (2)

13. Temperature *(Oral)*

a. Degrees: ___ ___ ___ • ___

b. Scale:

Fahrenheit (1)
Centigrade (2)

14. Blood pressure

a. Systolic: ___ ___ ___
mmHg

b. Diastolic: ___ ___ ___
mmHg

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

16. Respiratory rate: ___ ___
breaths/minute

C. Examination findings

17. Skin:

Normal (1)
20.
Abnormal (2)

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

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

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

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

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

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

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

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

_____

e. None of the above: (1)

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

Normal (1)
22.
Abnormal (2)

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

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

_____
specify

22. Neck:

Normal (1)
23.
Abnormal (2)

specify abnormality

23. Lymphatic:

Normal (1)
24.
Abnormal (2)

specify abnormality

24. Chest and lungs:

Normal (1)
25.
Abnormal (2)

specify

25. Heart:

Normal (1)
26.
Abnormal (2)

specify abnormality

26. Abdomen:

Normal (1)
28.
Abnormal (2)

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

a. Ascites: (1)

b. Obese: (1)

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

specify

28. Liver and spleen:

Normal (1)
30.
Abnormal (2)

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

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

____ ____ • ____
cm

b. Splenomegaly: (1)

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

specify

30. Extremities:

Not performed (0)
32.
Normal (1)
32.
Abnormal (2)

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

a. Contractures: (1)

b. Muscle wasting: (1)

c. Palmar erythema: (1)

d. Pedal edema: (1)

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

specify

32. Genitourinary/pelvis:

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

specify

33. Nervous system:

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

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

a. Mental status abnormal: (1)

b. Asterixis: (1)

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

_____
specify

D. Tanner Staging

35. Is Tanner staging required for this participant *(Note: Required at screening visit.) (check only one):*

Yes, participant has not reached full sexual maturity or is 17 years old or younger: (1)

No, participant is over 17 years old or had reached full sexual maturity *(Tanner stage 5 on all parameters at screening or for 2 consecutive visits)* (2)

44.

36. Is the patient female: Yes (1) No (2)

40.

Male Tanner Staging

37. Genital stage: ____
1-5

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

39. Pubic hair stage: ____
1-5

44.

Female Tanner Staging

40. Breast stage: ____
1-5

41. Pubic hair stage: ____
1-5

42. Has menarche occurred: Yes (1) No (2)

44.

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

____ ____
age in years

E. Ability to swallow study medication

(At the randomization visit the Study Physician/Clinical Coordinator will be asked to provide assurance that the patient is able to swallow the TONIC study medication; if needed, you could ask the patient to swallow a capsule from the placebo metformin provided by the DCC).

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

Yes, patient was able to swallow capsule (1)

No, patient was unable to swallow the capsule (2)

Elig

Did not ask for a demonstration at this time (3)

F. Administrative information

45. Study Physician PIN: ___ ___ ___

46. Study Physician signature:

_____

47. Clinical Coordinator PIN: ___ ___ ___

48. Clinical Coordinator signature:

_____

49. Date form reviewed:

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

TONIC

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.
When: Visits f004, f012, f024, f036, f060, f072, and f084.
Administered by: Study Physician and Clinical Coordinator.
Respondent: Patient.
Instructions: Details of the protocol for height, weight, waist and hip measurement are found in the TONIC SOP Part I. In brief: height, weight, waist and hips should be measured with the patient standing and wearing light clothing. Shoes should be removed for height and weight measures. Measure the waist around the abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line. Repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other. Measure the hips at the fullest part. Repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: p f 1

7. Study: TONIC 3

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

10. Waist *(standing, at midpoint between highest point of iliac crest and lowest part of costal margin; repeat waist measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

11. Hip *(standing, at fullest part of the hips; repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:

Fahrenheit: (1)
Centigrade: (2)

13. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

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

15. Respiratory rate: ____ ____ breaths/minute

C. Liver signs

16. Liver and spleen:

Normal (1)

18. ____

Abnormal (2)

17. Abnormality *(check all that apply)*

a. Ascites: (1)

b. Asterixis: (1)

c. Contractures: (1)

d. Hepatomegaly: (1)

If Yes, span from right midclavicular line:

____ ____ • ____ ____ cm

e. Jaundice: (1)

f. Muscle wasting: (1)

g. Palmar erythema: (1)

h. Pedal edema: (1)

i. Spider angiomata: (1)

j. Splenomegaly: (1)

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

_____
specify abnormality

D. Administrative information

18. Study Physician ID: ____ ____ ____

19. Study Physician signature:

_____

20. Clinical Coordinator ID: ____ ____ ____

21. Clinical Coordinator signature:

_____

22. Date form reviewed:

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

TONIC

RG - Registration

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

When: At first screening visit (s1).

Administered by: Clinical Coordinator.

Respondent: Patient and guardian.

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

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: s 1 ____ ____

6. Form & revision: r g 1

7. Study: TONIC 3

B. Consent

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

Yes (1) No (2)

STOP

9. Has the patient's guardian signed the TONIC informed consent statement:

Yes (1) No (2)

STOP

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

Yes (1)
No (2)

STOP

Not using assent (3)
Not using assent for this age child (4)

C. Information about patient

11. Date of birth:

____ ____–____ ____ ____–____ ____ ____ ____
day month year

Record 4-digit year for date of birth.

12. Age at last birthday: ____ ____
years

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

Yes (1) No (2)

Elig

14. Gender:

Male (1)
Female (2)

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

Hispanic or Latino or Latina (1)
Not Hispanic, not Latino, not Latina (2)

17.

16. What describes the patient's Hispanic, Latino, or Latina origin best *(show the patient/guardian Flash Card #1 and ask the respondent to pick the subcategory that best describes the patient's Hispanic, Latino, or Latina origin; check only one):*

Mexican	(1)
Puerto Rican	(2)
Cuban	(3)
South or Central American	(4)
Other Spanish culture or origin	(5)

_____
specify

17. Racial category *(show the patient/guardian Flash Card #2 and ask the respondent to pick the category or categories that describe the patient best; check all that apply)*

a. American Indian or Alaska Native:	(1)
b. Asian:	(1)
c. Black, African American, Negro, or Haitian:	(1)
d. Native Hawaiian or other Pacific Islander:	(1)
e. White:	(1)
f. Patient refused:	(1)

18. In what country was the patient born *(check only one):*

Continental US (includes Alaska) or Hawaii	(1)
Other, *(specify):*	(2)

_____
specify

19. Patient's current grade level in school (or home school) *(show the patient/guardian Flash Card #3 and ask the respondent to pick the category that describes the patient best; if summer time, report grade entering in the fall; check only one):*

Grades 1 to 5	(1)
Grades 6-8	(2)
Grades 9-12	(3)

20. Current age of patient's female guardian *(mother, stepmother, or other) (show patient/guardian Flash Card #4; check only one):*

Not applicable (mother is deceased or patient has no stepmother or female guardian)	(0)
19 or younger	(1)
20-29 years	(2)
30-39 years	(3)
40-49 years	(4)
50-59 years	(5)
60 years or older	(6)

21. Highest educational level achieved by patient's female guardian *(mother, stepmother, or other) (show patient/guardian Flash Card #5; if education of female guardian is unknown, record as "n"; check only one):*

Never attended school	(0)
Did not complete high school	(1)
Completed high school	(2)
Some college or post high school education or training	(3)
Bachelor's degree or higher	(4)

22. Current age of patient's male guardian *(father, stepfather, or other) (show patient/guardian Flash Card #4; check only one):*

Not applicable (father is deceased or patient has no stepfather or male guardian)	(0)
19 or younger	(1)
20-29 years	(2)
30-39 years	(3)
40-49 years	(4)
50-59 years	(5)
60 years or older	(6)

23. Highest educational level achieved by patient's male guardian *(father, stepfather, or other) (show patient/guardian Flash Card #5; if education of male guardian is unknown, record as "n"; check only one):*

Never attended school	(0)
Did not complete high school	(1)
Completed high school	(2)
Some college or post high school education or training	(3)
Bachelor's degree or higher	(4)

24. Combined annual income before taxes of all members of patient's household *(show guardian Flash Card #6 and ask respondent to pick the category that describes the patient's combined household income best; check only one):*

Less than $15,000	(1)
$15,000 - $29,999	(2)
$30,000 - $49,999	(3)
$50,000 or more	(4)

D. Source of patient

(Clinic staff should pick the best description of the source of patient)

25. Source of patient *(check only one):*

Bariatric surgery clinic	(01)
Current patient of NASH CRN investigator	(02)
Diabetes clinic	(03)
GI/liver clinic	(04)
HMO-based	(05)
Lipid disorders clinic	(06)
Obesity clinic	(07)
Pediatric clinic	(08)
Pediatric weight disorders clinic	(09)
Primary care clinic	(10)
Self referral	(11)
Other, *(specify):*	(12)

_____
specify

E. Previous registration in a NASH CRN study

26. Has the patient ever been assigned an ID number in a NASH CRN study:

(Yes 1) (No 2)

30.

27. In which NASH CRN studies has the patient previously been registered *(check all that apply)*

a. NAFLD Database:	(1)
b. Other, *(specify):*	(1)

_____
specify

28. ID Number previously assigned to patient *(record patient ID in item 2):*

___ ___ ___ ___

29. Code previously assigned to patient *(record patient code in item 3):*

___ ___ ___

31.

F. ID assignment

(If a STOP or ineligible condition was checked in section B, the patient is ineligible and a Patient ID should not be assigned. If the patient was previously registered in a NASH CRN study, a new ID number should not be assigned.)

30. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####,zzz

G. Administrative information

31. Clinical Coordinator PIN: ___ ___ ___

32. Clinical Coordinator signature:

_____

33. Date form reviewed:

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