BC - Blood Collection for DNA

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

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

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

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

| A. Center, patient and visit identification | C. Specimen for Genetics Repository |
|---|--|
| 1. Center ID: | Attach ID labels to two 10mL EDTA tubes and fill each with whole blood; invert each tube gently 6 times to mix blood with additives; keep tubes at room temperature until the same day shipment to |
| 2. Patient ID: | the NIDDK Genetics Repository. |
| 3. Patient code: | 10. Was blood collected for the NIDDK Genetics Repository: |
| 4. Date of visit: | Yes (1) |
| day mon year | No, (specify): |
| 5. Visit code: | specify |
| 6. Form & revision:bc1 | 15. |
| 7. Study: TONIC <u>3</u> | 11. Date and time of blood draw a. Date: |
| B. Check on consent | day mon year b. Time: |
| 8. Did the patient/parent consent/assent to blood draw for DNA extraction: | $\phantom{aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa$ |
| $\binom{\text{Yes}}{1} \qquad \binom{\text{No}}{*}_{2}$ | 12. Number of 10 mL EDTA tubes: |
| (STOP)—— | 13. Form copy of tube labels: |
| * You cannot proceed until you get consent. | TONIC Form BC |
| 9. Did the patient previously provide blood | Pt: ccc- 9999, xyz |
| for DNA banking in the NAFLD Database: | Gender Age, yrs.: XX |
| | 14. Phlebotomist: |
| | print name |

15. Clinical Coordinator PIN: ____ ___

16. Clinical Coordinator signature:

17. Date form reviewed:

day mon year

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 $\frac{1}{2}$ is checked for an item, use caution. If the physician agrees with the diagnosis, the patient is ineligible for TONIC. If we 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 **10.** Do any of the patient's first degree relatives (parent, brother, sister) have 1. Center ID: cirrhosis: 2. Patient ID: **3.** Patient code: 11. If yes, is the cause of the cirrhosis unknown (cryptogenic): **4.** Visit date (date this form is initiated): day mon year 12. Do any of the patient's first degree relatives (parent, brother, sister) have 5. Visit code: diabetes (Type 1 or Type 2): Yes **6.** Form & revision: <u>b g 1</u> No Don't know 7. Study: TONIC 3 13. Do any of the patient's first degree relatives (parent, brother, sister) have **B.** Family history obesity: **8.** Do any of the patient's first degree Yes relatives (parent, brother, sister) have No liver disease: Don't know 14. Do any of the patient's first degree relatives (parent, brother, sister) have atrophy of body fat: **9.** If yes, characterize the liver disease(s) (check all that apply) Yes **a.** Alcohol related liver disease: 1) No Don't know 1) **b.** Viral hepatitis:

c. Alpha-1 antitrypsin deficiency:

f. Hemochromatosis or iron overload:

g. Fatty liver disease (NAFLD, NASH):

h. Type of liver disease unknown:

e. Glycogen storage disease:

d. Wilson's disease:

1)

Yes

No

Don't know

15. Do any of the patient's first degree relatives (parent, brother, sister) have a

problem with cholesterol or blood fat:

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:
 - **c.** During a routine or insurance physical examination:
 - **d.** Blood donation:
 - e. Other (specify):

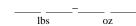
specify

- **18.** What procedures/tests supported this first diagnosis (*check all that apply*)
 - **a.** Liver biopsy: (1)
 - **b.** Imaging studies (*Ultrasound*, *CT*, *MRI*): (
 - **c.** Elevated aminotransferases: (1)
 - **d.** Other (specify):

specify

D. Weight history

19. What was the patient's birthweight:



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:

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):



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):

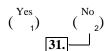
years

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:



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

Yes (No 2)

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

age in years

| 30. Characterize the menstrual history in the past year (<i>check only one</i>): | o. Other gastrointestinal bleeding: | (1) |
|--|---|-------------------------|
| Regular periods | p. Biliary diversion: | (₁) |
| Irregular periods | (1) (2) (Metabolic acidesis: | <u>/C\</u> — |
| Rare periods | q. Metabolic acidosis: | (1 |
| No periods | (₄) | $\overline{\mathbb{C}}$ |
| - | r. Ascites: | (1 |
| G. Medical history (means Caution; cond exclusionary if study physician agrees with nosis) | ition is a diag- s. Edema: | <u>⟨C</u> \ |
| 31. Has the patient ever been diagnosed with | t. Hepatic encephalopathy: | (₁) |
| or treated for any of the following (check a that apply; source of information can be interview and/or chart review) | u. Portal hypertension: | |
| a. Diabetes type 1: | | <u>/C\</u> |
| \sqrt{C} | v. Hepatorenal syndrome: | |
| b. Diabetes type 2: | | <u>/C\</u> — |
| \C\ | w. Hepatopulmonary syndrome: | |
| c. Gestational diabetes | | <u>/C\</u> |
| (diabetes of pregnancy): | (₁) x. Short bowel syndrome: | |
| d. Hepatitis B: | (1) | <u>/C\</u> |
| <u>/C\</u> | y. Hemophilia (bleeding disorder): | |
| e. Hepatitis C: | (1) | <u>/C\</u> |
| <u>/C\</u> | z. Systemic autoimmune disorder so rheumatoid arthritis or systemic l | |
| f. Autoimmune hepatitis: | aa. Endocrine disease | mpus. (1) |
| <u>/C</u> | (hormonal abnormality): | (1) |
| g. Autoimmune cholestatic liver disorder (PBC or PSC): | ab. Hepatocellular carcinoma: | (1) |
| C | | $\langle c \rangle$ |
| h. Wilson's disease: | () ac. Other malignancy (cancer): | (1) |
| (c) | | <u>c</u> |
| i. Alpha-1-antitrypsin (A1AT) | ad. Human immunodeficiency viru | S |
| deficiency: | (HIV): | (1 |
| \sqrt{c} | | $\langle C \rangle$ |
| j. Hemochromatosis or iron overload: | (ae. Peripheral neuropathy: | (1) |
| <u>/C</u> \ | af. Seizure disorder or epilepsy: | (1) |
| k. Drug induced liver disease: | ag. Drug allergies: | (1) |
| \C\ | ah. Hypothyroidism: | (1) |
| l. Gilbert's syndrome: | (₁) ai. Hypertension: | (1) |
| m. Esophageal or gastric varices on | aj. Cerebrovascular disease: | (1) |
| endoscopy: | ak. Dysbetalipoproteinemia: | (|
| /C\ | | (-) |

n. Bleeding from varices:

| | al. Hyperlipidemia (high cholesterol, high triglycerides): | (| 1) | 33. Is the patient currently undergoing evaluation for bariatric surgery: |
|-----|--|----------|------------------|---|
| | am. Pancreatitis: | (| 1) | Yes |
| | an. Cholelithiasis: | <u>c</u> | ₁) | |
| | ao. Coronary artery disease: | <u>(</u> | ₁) | 34. Has the patient received total parenteral nutrition (TPN) in the past 3 years: |
| | ap. Congestive heart failure: | <u>c</u> | _ ₁) | (Yes Light 1) Fig. |
| | aq. Elevated uric acid such as gout: | (| 1) | 35. Organ, limb, or bone marrow transplant |
| | ar. Kidney disease: | <u>c</u> | ₁) | a. Has the patient ever received a liver transplant: |
| | as. Polycystic ovary syndrome: | (| 1) | Yes |
| | at. Sleep apnea (not breathing during sleep): | (| 1) | |
| | au. Dermatologic disorders: | (| 1) | b. Has the patient ever received any |
| | av. Myopathy: | (| 1) | other organ, limb, or bone marrow transplant: |
| | aw. Myositis: | (| 1) | $\begin{pmatrix} \operatorname{Yes} & & & \\ & & 1 \end{pmatrix}$ |
| | ax. Major depression: | (| 1) | (1) |
| | ay. Schizophrenia: | (| 1) | H. Drugs historically associated with NAFLD |
| | az. Bipolar disorder: | (| 1) | 36. Has the patient used any tetracyclines, |
| | ba. Obsessive compulsive disorder: | (| 1) | salicylates, or valproic acid in the past 2 years (check all that apply) |
| | bb. Severe anxiety or personality disorder: | (| 1) | a. Acetylsalicylic acid (ASA): |
| | bc. Substance abuse: | (| 1) | b. Aspirin - 325 mg: |
| | be substance addse. | (c)- | 」 ¹ / | c. Demeclocycline (Declomycin): |
| | bd. None of the above: | (| 1) | d. Divalproex (Depakote): |
| | | | 1/ | e. Doxycycline (Monodox): |
| 32. | Has the patient ever had bariatric surg for any of the following (check all the | | | f. Minocycline (Dynacin, Minocin): |
| | a. Stapling or banding of the stomach | | , | g. Oxytetracycline (Terramycin): |
| | a. Stapfing of banding of the stomach | 6- | 」 ¹) | h. Tetracycline (Achromycin): |
| | b. Jejunoileal (or other intestinal) | 701 | | i. Valproate sodium (Depacon): |
| | bypass: | (| (1) | j. Valproic acid (Depakene): |
| | | <u></u> | _ | k. Other known hepatotoxin (specify): |
| | | , | ` | |
| | c. Biliopancreatic diversion: | <u>c</u> | 」 ¹) | l. None of the above: |

e. None of the above:

(1)

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



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

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

| a. | Betamethasone | sodium | (Celestone): | (| 1) |
|----|---------------|--------|--------------|---|----|
|----|---------------|--------|--------------|---|----|

| j. Other, (specify): | (| 1) |
|---|---|----|
| - · · · · · · · · · · · · · · · · · · · | | |

| k. Other, (specify): | (| 1/ |
|-----------------------------|---|----|
| | | |

| I. None of the above: | (| |
|------------------------------|---|----|
| 1. I tone of the above. | (| 1/ |

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

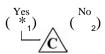


*Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past 2 years is exclusionary. **40.** Has the patient taken any anabolic steroids or tamoxifen in the past 2 years (*check all that apply*)

| a. Boldenone undecylenate | (Equipoise): | (| 1) |
|---------------------------|--------------|---|------|
| | / T. I | • | - 17 |

| m. None of the above: | (| ` |
|------------------------------|---|----|
| III. Nolle of the above. | (| 1. |

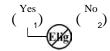
41. Were any of the items 40a-l checked:



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

I. Use of antidiabetic drugs

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



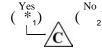
43. Has the patient used any antidiabetic medications in the past 3 months (*check all that apply*):

| ose (Precose): | (| 1 |
|----------------|---|---|
| ose (Precose): | (| |

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

| · | | |
|--------------------|---|----|
| None of the above: | (| 1) |

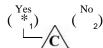
44. Were any of the items 43a-p checked:



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

J. Use of antiNAFLD drugs and vitamins

- **45.** Has the patient taken any of these antiNAFLD drugs in the past 3 months (*check all that apply*)
 - **a.** Betaine (Cystadone): (1)
 - **b.** Choline + methionine + betaine + adenosine + pyridoxine (Epocler): (1)
 - **c.** Metformin: (1)
 - **d.** Ursodeoxycholic acid (UDCA, Actigall, URSO, Ursodiol):
 - **e.** S-Adenylmethionine (SAM-e):
 - **f.** Milk thistle: (1)
 - **g.** Probiotics (any form): (1)
 - **h.** Gemfibrozil (Gen-Fibro, Lopid):
 - i. None of the above:
- **46.** Were any of item 45a-h checked:

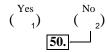


*Caution: Use of antiNAFLD drugs in the 3 months prior to randomization is exclusionary.

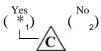
47. Has the patient taken a multivitamin regularly in the past 3 months:

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

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

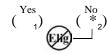


49. Was/Is the dose of vitamin E greater than 100 IU/day:



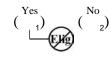
*Caution: Use of vitamin E at more than 100 IU/day in the 3 months prior to randomization is exclusionary.

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



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

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



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

| a. Vitamin B | (any type): |
|--------------|-------------|
|--------------|-------------|

| 1 | ` |
|---|----|
| (| 1) |
| • | 1/ |

| 1 | \ |
|---|-----|
| | 1) |
| (| . 1 |
| ` | 1/ |

| (| 1 |
|---|----|
| (| 1) |

| (| .) |
|---|-----|
| (| .) |

| e. | None | of the | ahove |
|----|------|--------|-------|

| 1 | ` |
|---|-----|
| (| ٠,) |

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 | (Li | pitor) |
|-----------------|-----|--------|
|-----------------|-----|--------|



| b. | Colestipo | l hydrochloride | (Colestid): |
|----|-----------|-----------------------|-------------|
| | Colesupo | i ii y di Ocilioi ide | (Colobina). |

| 1 | 1 |
|---|----|
| (| 1) |

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

| ` | 1/ |
|---|----|
| | |
| | |

J. Francisco (Trine)

| 1) |
|----|
| |

d. Fenofibrate (Tricor):

| 1) |
|----|
| |

e. Fluvastatin sodium (Lescol):

| ` |
|----|
| 1) |

f. Lovastatin (Mevacor):

| 1/ | |
|----|--|
| ` | |

g. Nicotinic acid (Niaspan):

| 1) | |
|----|--|
| | |

g. Meonine dela (Maspan).

| 1 | ` |
|---|----|
| (| 1) |

h. Pravastatin sodium (Pravachol):

| 1 | ` |
|---|----|
| (| .) |

i. Rosuvastatin (Crestor):

| , | | ١ |
|---|---|---|
| | 1 |) |

j. Simvastatin (Zocor):

| 1 | ١ |
|---|----|
| (| ,) |

k. Other, (specify):

| | 17 |
|---|----|
| 1 | ` |
| (| |

| - | | | |
|----|------|--------|--------|
| I. | None | of the | above: |

| (| 1) |
|---|----|
| ` | 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):

- $\begin{pmatrix} & & \\ & & 1 \end{pmatrix}$
- **e.** Phendimetrazine tartrate (Adipost, Bontril):
- (1)
- **f.** Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine):
 - (1)
- **g.** Sibutramine hydrochloride monohydrate (Meridia):

h. Other, (specify):

| ` | 17 |
|---|----|
| (|) |

i. Other, (specify):

| (|) |
|----|---|
| ١. | |

j. None of the above:

| / | ` |
|---|---|
| (| 1 |

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



*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/ |
|-------------------------------|---|----|
| 6. Aspirin - 325 mg: | (| 1/ |
| c. Celecoxib (Celebrex): | (| 1/ |
| d. Ibuprofen (Advil, Motrin): | (| 1, |
| e. Indomethacin (Indocin): | (| 1/ |
| . Naproxen (Aleve, Naprosyn): | (| 1/ |
| g. Other, (specify): | (| 1/ |
| | | |

| i. None of the above: | (| 1) |
|-----------------------|---|----|

1)

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

h. Other, (specify):

| 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 |

| Other, (specify): | (| 1) |
|-------------------|---|----|
| 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/ |
| i. None of the above: | (| , |

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) |

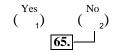
60. Has patient taken any of the following medications in the past 3 months (*check all that apply*)

| a. Isotretinoin (Accutane): | 1 |) |
|------------------------------------|---|---|
|------------------------------------|---|---|

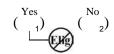
| m. None of the above: | (| 1 |
|------------------------------|---|---|
| | ` | 1 |

M. Willingness to use effective birth control methods

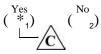
61. Are you female and of childbearing potential:



62. Are you currently pregnant:



63. Are you currently breast feeding:

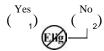


*Caution: Patient cannot be breastfeeding at time of randomization.

z. None of the above:

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

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



N. Administrative information

| 65. | Study | Physician | PIN: | | | |
|------------|-------|-----------|------|--|--|--|
|------------|-------|-----------|------|--|--|--|

66. Study Physician signature:

| 67 | Clinical | Coordinator | PIN | |
|-----|----------|-------------|-------|--|
| W/. | Cillical | Coordinator | FIIN. | |

- **68.** Clinical Coordinator signature:
- ____
- **69.** Date form reviewed:

| day | mon | year |
|-----|-----|------|

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

| Α. | Center. | visit. | and | patient | identification |
|----|---------|--------|-----|---------|----------------|
| | | | | | |

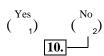
- **1.** Center ID: ____ ___ ___
- **2.** Patient ID: ____ ___ ___
- **3.** Patient code: ____ ___
- **4.** Visit date (date this form is initiated):

| _ | | _ |
|-----|-----|------|
| 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:



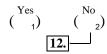
9. If yes, characterize the liver disease(s) (*check all that apply*)

| a. Alcohol related liver disease: | (| 1) |) |
|--|---|----|---|
|--|---|----|---|

Other (specify).

specify

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



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

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

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

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

| 14. | Do any of the patient's first degree 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) |
| . N | AFLD history | | |
| 16. | Date patient was first diagnosed with nonalcoholic fatty liver disease (NAFLD): | /ear | |
| ١7. | 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 (<i>Ultrasound</i> , <i>CT</i> , <i>MRI</i>). | . (| 1) |
| | c. Elevated aminotransferases: | (| .) |

specify

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:

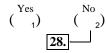
age in years

E. Tobacco cigarette smoking history

(interview with patient; not by chart review)

23. Have you ever smoked tobacco cigarettes:

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):



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

d. Other (*specify*):

1)

F. Menstrual history

28. Is the patient female:

| Yes | No | |
|-----------------------------------|-----|---|
| $\begin{pmatrix} 1 \end{pmatrix}$ | (2 |) |
| | 31. | |

- **29.** Menarche history
 - a. Has menarche occurred:

| Yes | No |
|-----------------------------------|--|
| $\begin{pmatrix} 1 \end{pmatrix}$ | $\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$ |
| | 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 (hears Caution; condition is exclusionary if study physician agrees with diagnosis)
- **31.** Has the patient ever been diagnosed with or treated for any of the following (check all that apply; source of information can be interview and/or chart review)

| a. Diabetes type 1 | : |
|---------------------------|---|
|---------------------------|---|



b. Diabetes type 2:

| \triangle | (| 1) |
|-------------|---|----|
| /C\ | _ | _ |

c. Gestational diabetes (diabetes of pregnancy):

| | • | 1/ |
|----------|---|-----|
| \wedge | (| (1) |

d. Hepatitis B:

e. Hepatitis C:

| /C\ | | |
|----------|---|----|
| <u>c</u> | (| 1) |

f. Autoimmune hepatitis:

| \triangle | (| | 1) |
|-------------|---|---|----|
| (C) | | _ | |

g. Autoimmune cholestatic liver disorder

| ratommune enoiestatie nver disorder | | |
|-------------------------------------|--------|----------------|
| (PBC or PSC): | ((| ₁) |
| | | |

h. Wilson's disease:



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



j. Hemochromatosis or iron overload:



k. Drug induced liver disease:



I. Gilbert's syndrome:



m. Esophageal or gastric varices on endoscopy:



n. Bleeding from varices:



| | () | | | |
|---|------------------|--|-------------|----|
| o. Other gastrointestinal bleeding:p. Biliary diversion: | (₁) | al. Hyperlipidemia (high cholesterol, high triglycerides): | (| 1) |
| p. Binary diversion. | | am. Pancreatitis: | (| 1) |
| q. Metabolic acidosis: | () | an. Cholelithiasis: | (| 1) |
| q. Metabolic acidosis. | C | | <u>C</u> | |
| r. Ascites: | (₁) | ao. Coronary artery disease: | (C) | 1) |
| s. Edema: | (₁) | ap. Congestive heart failure: | | 1) |
| t. Hepatic encephalopathy: | (₁) | aq. Elevated uric acid such as gout: | (| 1) |
| u. Portal hypertension: | () | ar. Kidney disease: | (| 1) |
| u. I oftal hypottension. | C | | <u>C</u> | |
| v. Hepatorenal syndrome: | (,) | as. Polycystic ovary syndrome: | (| 1) |
| | <u>c</u> | at. Sleep apnea (not breathing during sleep): | (| 1) |
| w. Hepatopulmonary syndrome: | (1) | au. Dermatologic disorders: | (| 1) |
| | <u>C</u> | av. Myopathy: | (| 1) |
| x. Short bowel syndrome: | (₁) | aw. Myositis: | (| 1 |
| | <u> </u> | ax. Major depression: | (| 1) |
| y. Hemophilia (bleeding disorder): | | ay. Schizophrenia: | (| 1) |
| | <u>/C\</u> | az. Bipolar disorder: | (| 1) |
| z. Systemic autoimmune disorder suc rheumatoid arthritis or systemic lu | | ba. Obsessive compulsive disorder: | (| 1) |
| aa. Endocrine disease (hormonal abnormality): | (₁) | bb. Severe anxiety or personality disorder: | (| 1) |
| ab. Hepatocellular carcinoma: | (| bc. Substance abuse: | <u>c</u> | 1) |
| ac. Other malignancy (cancer): | | bd. None of the above: | (| 1) |
| ad. Human immunodeficiency virus | <u>/C\</u> | 32. Has the patient ever had bariatric surg for any of the following (<i>check all the</i> | | |
| (HIV): | | a. Stapling or banding of the stomach | i: (| 1) |
| ae. Peripheral neuropathy: | (1) | b. Jejunoileal (or other intestinal) | | |
| af. Seizure disorder or epilepsy: | (1) | bypass: | (| 1) |
| ag. Drug allergies: | (1) | | <u>C</u> | |
| ah. Hypothyroidism: | (1) | c. Biliopancreatic diversion: | (| 1) |
| ai. Hypertension: | (1) | | <u>/C</u> \ | |
| aj. Cerebrovascular disease: | (1) | d. Other GI or bariatric surgery (spec | ify): (| 1) |
| ak. Dysbetalipoproteinemia: | (1 | | | |
| | <u></u> | e. None of the above: | (| 1) |

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



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



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



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



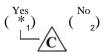
H. Drugs historically associated with NAFLD

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

| a. | Acetylsalicylic acid (ASA): | (| ,) |
|----|-------------------------------------|---|----|
| | 1 10003 1541103 110 4010 (1 151 1). | • | 1/ |

| - | | |
|-----------------------|---|----|
| l. None of the above: | (| 1) |
| I. None of the above: | (| 1/ |

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



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

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

| a. Betamethasone sodium (Celestone): | (| ` |
|--|---|----|
| a. Detainethasone soulum (Celestone). | (| 1. |

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



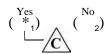
*Caution: Use of systemic glucocorticoids for more than 2 consecutive weeks in the past 2 years is exclusionary.

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

| a. Boldenone undecylenate | (Equipoise): | (1) |) |
|---------------------------|--------------|------|---|
|---------------------------|--------------|------|---|

| l. Other, (specify): | (| 1) |
|-----------------------------|---|-----|
| | , | 1.7 |

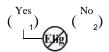
41. Were any of the items 40a-l checked:



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

I. Use of antidiabetic drugs

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

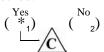


43. Has the patient used any antidiabetic medications in the past 3 months (*check all that apply*):

| .) |
|----|
| |

q. None of the above:
$$\begin{pmatrix} & & \\ & & \end{pmatrix}$$

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



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

J. Use of antiNAFLD drugs and vitamins

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

| (| |
|---|---|
| | (|

h. Gemfibrozil (Gen-Fibro, Lopid):
$$\binom{1}{1}$$

| specify | |
|---------|--|

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

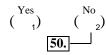


1)

*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:

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

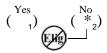


49. Was/Is the dose of vitamin E greater than 100 IU/day:



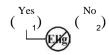
*Caution: Use of vitamin E at more than 100 IU/day in the 3 months prior to randomization is exclusionary.

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



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

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



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

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*):

b. Colestipol hydrochloride (Colestid):
$$\binom{1}{1}$$

| 55. | Were any of the items 54a-i checked: | N | √o ′ |
|-----|--|---|------|
| | j. None of the above: | (| 1) |
| | i. Other, (specify): | (| 1) |
| | h. Other, (specify): | (| 1) |
| | g. Sibutramine hydrochloride monohydrate (Meridia): | (| 1) |
| | f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): | (| 1) |
| | e. Phendimetrazine tartrate (Adipost, Bontril): | (| 1) |
| | d. Orlistat (Xenical): | (| 1) |
| | c. Methamphetamine hydrochloride (Desoxyn, Gradumet): | (| 1) |
| | b. Fenfluramine hydrochloride (Pondimin): | (| 1) |
| | a. Dexfenfluramine hydrochloride (Redux): | (| 1) |
| 54. | Has the patient taken any antiobesity medications in the past 3 months (check all that apply): | | |
| | | | |



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

| 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):

l. None of the above:

| 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: |

| 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. |
| i. None of the above: | (| |

| 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) |

| been reported on this form (check all th | чан аррі | <i>y)</i> |
|--|----------|------------|
| 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) |
| i. Fish oil (any form): | (| 1) |
| k. Flax seed oil: | (| 1) |
| I. Garlic: | (| 1) |
| m. Ginkgo biloba: | (| 1) |
| n. Glucosamine (any form): | (| 1) |
| o. Lecithin: | (| 1) |
| p. Magnesium: | (| 1) |
| q. N-acetyl-cysteine: | (| 1) |
| r. Potassium (any form): | (| 1) |
| s. Saw palmetto: | (| 1) |
| t. Selenium: | (| 1) |
| u. St. John's Wort: | (| 1) |
| v. Taurine: | (| 1) |
| w. Zinc picolinate: | (| 1) |
| x. Other, (specify): | (| 1) |
| y. Other, (specify): | (| 1) |
| | | |

z. None of the above:

(1)

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

| a. Isotretinoin (Accutane): (| 1 |) |
|--------------------------------------|---|---|
|--------------------------------------|---|---|

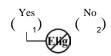
j. Other, (specify):
$$\begin{pmatrix} 1 \end{pmatrix}$$

M. Willingness to use effective birth control methods

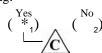
61. Are you female and of childbearing potential:



62. Are you currently pregnant:



63. Are you currently breast feeding:



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

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



N. Administrative information

| 65. | Study | Physician | PIN: | | |
|-----|-------|-----------|------|--|------|
| | | | | | |

69. Date form reviewed:

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

BP - Blood Processing for Plasma and Serum

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

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

By whom: Clinical Coordinator and laboratory personnel responsible for collection and processing of whole blood. **Instructions**: Put 2.7 mL of whole blood in CTAD tube and fill SST tubes with whole blood and prepare plasma and serum aliquots in the quantities specified below for the visit.

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

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

| A. Center, patient and vis | it identification | 6. Form & revision: | <u>b</u> <u>p</u> <u>1</u> |
|----------------------------|-------------------|----------------------------|----------------------------|
| 1. Center code: | | 7. Study: | TONIC_3_ |
| 2. Patient ID: | | | |
| 3. Patient code: | | | |
| 4. Date of visit: | | | |
| day | mon year | | |
| 5. Visit code: | | | |

B. Processing whole blood

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

8. Was blood collected for the NIDDK Biosample Repository:

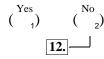
| Yes | (| 1) |
|--|-------------------|---------------------|
| No, patient was not fasting for 12 hours | (| 2) |
| No, other reason (specify): | 3. — (3. — |] ₃) |
| specify other reason | | |

specify other reason

9. Date and time of blood draw

| _ | day | mon | year |
|-----------------|--------|-----|-------|
| b. Time: | : | _ (|) (2 |
| hour | minute | am | pm |

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



11. Attach duplicate CTAD tube label:

| TONIC 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 9999, xyz Visit: vvvv BP Date: -

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

TONIC Serum 4 9999, xyz Pt: 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.

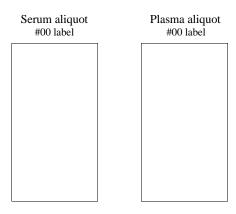
15. Date and time of separation into plasma and serum aliquots

a. Date: mon year **b.** Time: hour minute

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

17. Number of aliquots of serum:

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



19. Technician:

| | nri | nt 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: | | | |

- **21.** Number of cryovials frozen: ____ __

E. Administrative information

- 23. Clinical Coordinator PIN: ____ ___
- **24.** Clinical Coordinator signature:

CG - Genetic Consent Documentation

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

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

By whom: Study Physician and Clinical Coordinator.

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

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

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.

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

| _ Patient ID D. Histology |
|---|
| _ 15. Biopsy length (mm) |
| H & E stain |
| 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 (<i>central</i>); 1 =Zone 1 (<i>periportal</i>); 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 (<i>Kupffer cells</i>): 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 (<i>requires trichrome</i>); |
| 1b =Moderate, zone 3, perisinusoidal (<i>does not require trichrome</i>); 1c =Portal/periportal only; |
| 2 =Zone 3 and periportal, any combination; 3 =Bridging; 4 =Cirrhosis |
| |
| 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 mor |
| 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: |

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 identifica | tion | | 10. Place of death: | | |
|---|-------------------|-------------|---|------------|----------------|
| 1. Center ID: | | | city/state/country | | |
| 2. Patient ID: | | | city/state/country | | |
| 3. Patient code:4. Date form is initiated (date of notice) | e): | | 11. Cause of death (Study Physician: use whatever kn- have and your best medical judgment acterize the cause of death; check on | to best ch | you har- |
| | year | | Heart disease | (| 1) |
| day | ycai | | Stroke | (| 2) |
| 5. Visit code:n | | | Liver disease | (| 3) |
| | | | Malignancy | (| 4) |
| 6. Form & revision:d | _ <u>_r</u> | L | Other (specify): | (| ₅) |
| 7. Study: | 7. Study: TONIC 3 | | specify | | |
| B. Death information | | | specify | | |
| 8. Date of death: | | | Unknown | (| 6) |
| day mon | year | | C. Administrative information | | |
| 9. Source of death report (check all the | at apply): | | 12. Study Physician PIN: | | |
| a. Patient's family: | (| 1) | | | |
| b. Friend: | (| 1) | 13. Study Physician signature: | | |
| c. Health care provider or NASH C staff: | RN (| 1) | 14. Clinical Coordinator PIN: | | |
| d. Newspaper: | (| 1) | The chinear coordinator Fire. | · —— — | |
| e. Funeral parlor/home: | (| 1) | 15. Clinical Coordinator signature: | | |
| f. Medical record: | (| 1) | | | |
| g. Medical examiner: | (| 1) | 16. Date form reviewed: | | |
| h. Coroner: | (| 1) | 10. Date form reviewed. | | |
| i. Other (specify): | (| 1) | day mon | year | |
| other source | | | | | |

other source

Purpose: To record DEXA scan measurements.

DX - DEXA Scan for Body Fat

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 identif | ication | 10. DEXA scanner used: | |
|--|-----------|---|-------------------------------|
| 1. Center ID: | | Hologic QDR 4500A | (1) |
| 1. Center ID. | | Hologic QDR 4500W | (2) |
| 2. Patient ID: | | Hologic New Discovery Series 12.3 | (3) |
| Z. I defent ID. | | Hologic Delphi QDR Series | (4) |
| 3. Patient code: | | Hologic Delphi W | (5) |
| ev i allem es del | | Lunar Prodigy | (6) |
| 4. Date of visit: | | Other (specify) | (7) |
| day mon | year | | |
| 5. Visit code: | | specify make & model | |
| 5. Visit code. | | C. DEXA results summary | |
| 6. Form & revision: | _dx1_ | 11. Date of DEXA scan: | |
| 7. Study: | TONIC 3 | day mon | year |
| B. DEXA scan information | de dest | 12. Trunk % fat (if your scanner reports be fat and region % fat, record region % report): | oth tissue % 6 fat on this |
| 8. Did the patient have a whole bo energy x-ray absorptiometry (D scan: | | | <u>•</u> — |
| 10. | Yes No No | 13. Total % fat (if your scanner reports be fat and region % fat, record region % report): | oth tissue % 6 fat on this |
| 9. Specify why DEXA scan was neperformed | ot | | 6 |
| a. Patient is too heavy: | (1) | C. Administrative information | |
| b. Scanner is broken: | (1) | 14. Clinical Coordinator PIN: | |
| c. Other (specify): | (1) | 2 10 021111 0002 001 001 1 12 11 11 11 11 11 11 11 11 11 11 11 | |
| | , г | 15. Clinical Coordinator signature: | |
| specify | | | |
| | 14. | | |
| | | 16. Date form reviewed: | |
| | | | vear |

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 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

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

2. Patient ID:

| day | mon | year |
|-----|-----|------|

- **5.** Visit code: <u>r z ___ __ __</u>
- **6.** Form & revision: <u>e c 1</u>
- **7.** Study: TONIC <u>3</u>

B. Alcohol use exclusion

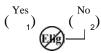
8. Does the patient have a history of significant alcohol intake:



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



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



C. Cirrhosis exclusion

- 11. Clinical cirrhosis evaluation
 - **a.** Does the patient have varices or ascites <u>and</u> does the Study Physician judge that the patient has cirrhosis:



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

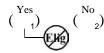


D. Other chronic liver disease exclusions

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



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



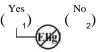
13. Does the patient have Wilson's disease defined by the ceruloplasmin below the lower limit of normal and liver histology consistent with Wilson's disease:



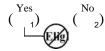
14. Does the patient have alpha-1 antitrypsin (A1AT) deficiency confirmed by A1AT level less than normal (*physician judgment*):



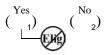
15. Does the patient have an iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy:



- **16.** Do any of the patient's assessments show evidence of other chronic liver disease
 - **a.** Drug induced liver disease as defined on the basis of typical exposure and history:



b. Known bile duct obstruction:

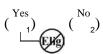


c. Any other type of liver disease other than NAFLD that warrants exclusion from the trial:

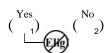


E. Other medical exclusions

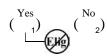
17. History of metabolic acidosis:



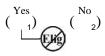
18. History of renal dysfunction:



19. History of coagulopathy:



20. History of diabetes mellitus:



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



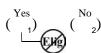
22. History of hepato-biliary surgery:



23. Inability to safely undergo liver biopsy:



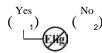
24. Use of drugs associated with NAFLD for more than 2 consecutive weeks in the 2 years prior to screening:



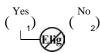
25. Use of antidiabetic drugs in the 3 months prior to randomization:



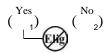
26. Use of antiNAFLD drugs in the 3 months prior to randomization:



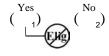
27. Use of antiobesity drugs in the 3 months prior to randomization:



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



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



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



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



F. Birth control exclusion

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

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

G. Check on ability to swallow study medication

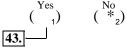
33. In your judgment (Study Physician/Clinical Coordinator), is the patient able to swallow the TONIC study medications (if you are unsure, you may ask the patient to swallow a capsule from the sample bottle of placebo metformin sent by the DCC prior to the start of TONIC):



H. Eligibility check on day of randomization

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

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



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

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

Yes

(1)

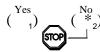
No

(2)

Task not run because patient is known to be ineligible

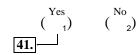
(3)

36. Does the patient feel well today:

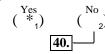


*Defer randomization until the patient feels well; when the patient returns to attempt randomization again, review all items on this form and update each item as needed.

37. Is the patient male:



38. Is the patient of childbearing potential:



*Administer pregnancy test.

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



*Go to item 43.

40. Is the patient currently breast feeding:



*Go to item 43.

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



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

specify reason

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



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

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

| I. Re | easons for ineligibility for ineligible patients. Note: Complete this section for ineligible patients. | | nts |
|-------|--|-----|-----|
| 43. | Reason for ineligibility (check all that app | ly) | |
| | 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 (<i>specify</i>): | (| 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.)

HI - Followup Medical History

Purpose: To record followup medical history information about the patient.

When: Visits f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.

Administered by: Clinical Coordinator, reviewed by Study Physician.

Respondent: Patient.

Instructions: Collect information by interview or chart review.

| A. Center, visit, and patient identification | D. Alcohol consumption (AUDIT-C) since the last visit (interview with patient) | | | |
|--|---|---|--|--|
| 1. Center ID: | Tible (merview with patterns) | | | |
| 2. Patient ID: | 11. Since the last visit, how often have you had a drink containing alcohol: | | | |
| 2. I dicit iD | Never (0) |) | | |
| 3. Patient code: | 14. | | | |
| 3. Fatient code | Monthly or less (1) |) | | |
| 4. Visit date: | Two to four times a month (2) |) | | |
| 4. Visit date. | Two to three times a week (3) | | | |
| day mon year | Four or more times a week (4) |) | | |
| 5. Visit code: | 12. Since the last visit, how many drinks containing alcohol did you have on a typical day when you are drinking: | | | |
| 6. Form & revision:hi1 | 1 or 2 |) | | |
| 7 (4) | 3 or 4 (₁) | | | |
| 7. Study: TONIC <u>3</u> | 5 or 6 (₂) | | | |
| D. I., 4 | 7 to 9 (₃) | | | |
| B. Interval identification | 10 or more |) | | |
| 8. Date of last Followup Medical History form (<i>if this is visit f004 then date of s1</i>): | 13. Since the last visit, how often have you had six or more drinks on one occasion: | | | |
| day mon year | Never (₀) |) | | |
| | Less than monthly (1) | | | |
| 9. Visit code of last Followup Medical History form (<i>if this is visit f004 then s1</i>): | Monthly (2) | | | |
| 1115tory 101111 (ij iius is visu joo4 ineit \$1). | Weekly (3) | | | |
| | Daily or almost daily (4) | | | |

C. NAFLD evaluation

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

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

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

| E. Tobacco cigarette smoking (interview with | | | | r. Ascites: | (| 1) |
|--|---|-------|------|--|---|----------------|
| patient) | | | | s. Edema: | (| 1) |
| 14. Since the last visit, have you smoked | | | | t. Hepatic encephalopathy: | (| 1) |
| | tobacco cigarettes regularly ("No" means less than I day per week on average): | | | u. Portal hypertension: | (| 1) |
| | Yes (1) | (N | lo) | v. Hepatorenal syndrome: | (| 1) |
| | 1/ [17. | ` | | w. Hepatopulmonary syndrome: | (| 1) |
| | | J | | x. Short bowel syndrome: | (| 1) |
| 15. | On average, how many days per week have you smoked cigarettes: | | | y. Hemophilia (bleeding disorder): | (| 1) |
| 16 | | # d | ays | z. Systemic autoimmune disorder such as rheumatoid arthritis or systemic lupus: | (| 1) |
| 10 | On the days that you smoked, about how many cigarettes did you smoke per day: | | | aa. Endocrine disease (hormonal abnormality): | (| ₁) |
| | | | | ab. Hepatocellular carcinoma: | (| 1) |
| | # cigarettes | per d | ay | ac. Other malignancy (cancer): | (| 1) |
| F. N | Aedical history | | | ad. Human immunodeficiency virus (HIV): | (| ₁) |
| 17 | Since the last visit, has the patient been diagnosed with or treated for any of the | | | ae. Peripheral neuropathy: | (| 1) |
| | following (check all that apply; source of | | | af. Seizure disorder or epilepsy: | (| 1) |
| | information can be interview and/or chart review) | | | ag. Drug allergies: | (| 1) |
| | a. Diabetes type 1: | (| 1) | ah. Hypothyroidism: | (| 1) |
| | b. Diabetes type 2: | (| 1) | ai. Hypertension: | (| 1) |
| | c. Gestational diabetes | | | aj. Cerebrovascular disease: | (| 1) |
| | (diabetes of pregnancy): | (| 1) | ak. Dysbetalipoproteinemia: | (| 1) |
| | d. Hepatitis B: | (| 1) | al. Hyperlipidemia (high cholesterol, | , | |
| | e. Hepatitis C: | (| 1) | high triglycerides): | (| 1) |
| | f. Autoimmune hepatitis: | (| 1) | am. Pancreatitis: | (| 1) |
| | g. Autoimmune cholestatic liver disorder | (|) | an. Cholelithiasis: | (| 1) |
| | (PBC or PSC): | (| 1) | ao. Coronary artery disease: | (| 1) |
| | h. Wilson's disease: | (| 1) | ap. Congestive heart failure: | (| 1) |
| | i. Alpha-1-antitrypsin (A1AT) deficiency: | (| 1) | aq. Elevated uric acid such as gout: | (| 1) |
| | j. Hemochromatosis or iron overload: | (| 1) | ar. Kidney disease: | (| 1) |
| | k. Drug induced liver disease: | (| 1) | as. Polycystic ovary syndrome: | (| 1) |
| | l. Gilbert's syndrome: | (| 1) | at. Sleep apnea (not breathing during sleep): | (| 1) |
| | m. Esophageal or gastric varices on endoscopy: | (| 1) | au. Dermatologic disorders: | (| 1) |
| | n. Bleeding from varices: | (| 1) | av. Myopathy: | (| 1) |
| | o. Other gastrointestinal bleeding: | (| 1) | aw. Myositis: | (| 1) |
| | p. Biliary diversion: | (| 1) | | | |
| | q. Metabolic acidosis: | (| 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) |
| 0 | Since the last visit has the nationt | | |

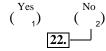
19. Since the last visit, has the patient received an organ, limb, or bone marrow transplant:

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

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

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

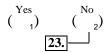
21. Since the last visit, has the patient been hospitalized:



If Yes, specify reason:

| specify |
|---------|

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



If Yes, specify:

| , I | | |
|-----|---------|--|
| | | |
| | | |
| | specify | |

G. Medication use

- **23.** Since the last visit, has the patient used any antidiabetic medications (*check all that apply*):
 - **a.** Acarbose (Precose):
 - **b.** Acetohexamide (Dymelor): (1)
 - **c.** Chlorpropamide (Diabinese):
 - **d.** Glimepiride (Amaryl): (1)
 - **e.** Glipizide (Glucotrol, Glucatrol XL): (1)
 - **f.** Glyburide (Micronase, DiaBeta, Glynase):
 - g. Insulin:
 - h. Metformin (Glucophage, Glucophage XR) (do not include TONIC study medication):
 - i. Miglitol (Glycet):
 - **j.** Nateglinide (Starlix):
 - **k.** Pioglitazone (Actos):
 - **l.** Repaglinide (Prandin): (1)
 - **m.** Rosiglitazone (Avandia):
 - **n.** Tolazamide (Tolinase):
 - **o.** Tolbutamide (Orinase):
 - **p.** Other, (*specify*): (1)
 - **q.** None of the above:

| 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/ |
| 25. | m. None of the above: Since the last visit, has the patient taken | (| 1/ |
| | | | |
| | any antiobesity medications (check all the | ıt app | ly). |
| | any antiobesity medications (check all thea. Dexfenfluramine hydrochloride (Redux): | at app (| ly). |
| | a. Dexfenfluramine hydrochloride | | |
| | a. Dexfenfluramine hydrochloride (Redux):b. Fenfluramine hydrochloride | (| 1/ |
| | a. Dexfenfluramine hydrochloride (Redux): b. Fenfluramine hydrochloride (Pondimin): c. Methamphetamine hydrochloride | (| 1/ |
| | a. Dexfenfluramine hydrochloride (Redux): b. Fenfluramine hydrochloride (Pondimin): c. Methamphetamine hydrochloride (Desoxyn, Gradumet): | (| 1/2 |
| | a. Dexfenfluramine hydrochloride (Redux): b. Fenfluramine hydrochloride (Pondimin): c. Methamphetamine hydrochloride (Desoxyn, Gradumet): d. Orlistat (Xenical): e. Phendimetrazine tartrate (Adipost, | (((| 1/2 |
| | a. Dexfenfluramine hydrochloride (Redux): b. Fenfluramine hydrochloride (Pondimin): c. Methamphetamine hydrochloride (Desoxyn, Gradumet): d. Orlistat (Xenical): e. Phendimetrazine tartrate (Adipost, Bontril): f. Phentermine hydrochloride (Adipex, | | 1/2 |
| | a. Dexfenfluramine hydrochloride (Redux): b. Fenfluramine hydrochloride (Pondimin): c. Methamphetamine hydrochloride (Desoxyn, Gradumet): d. Orlistat (Xenical): e. Phendimetrazine tartrate (Adipost, Bontril): f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): g. Sibutramine hydrochloride | | 1) |
| | a. Dexfenfluramine hydrochloride (Redux): b. Fenfluramine hydrochloride (Pondimin): c. Methamphetamine hydrochloride (Desoxyn, Gradumet): d. Orlistat (Xenical): e. Phendimetrazine tartrate (Adipost, Bontril): f. Phentermine hydrochloride (Adipex, Fastin, Ionamin, Teramine): g. Sibutramine hydrochloride monohydrate (Meridia): | | 1/2 |

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

| Y | es . | N | lo |
|---|------|---|----|
| (| 1) | (| 2) |

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

| Yes | No |
|-----------------------------------|------|
| $\begin{pmatrix} 1 \end{pmatrix}$ | (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 | No |
|---------|------|
| $(*_1)$ | (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 take any supplements (<i>check all that apply</i>) | | |
|---|---|----|
| 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) |

| 36. Since the last visit, has the patient taken any of the following medications or other supplements or medications (record all other plements or medications): | her s | ир- |
|---|-------|-----|
| 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) |

ae. None of the above:

(1)

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

H. Administrative information

day

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

mon

year

A

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), interview er administered (age 8-12). Clinical Coordinator must be available to answer questions and review for completeness.

Respondent: Patient, age 8 through 17. Patient age 13 or older should complete the form without help from family. Clinical Coordinator/parent should assist patient age 8-12.

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

| Ce | nter, patient, and vis | sit iden 1 | ificatio | n | | | dministrative information |
|----|------------------------|------------|----------|------------|------------|-----|--|
| 1. | Center ID: | | | · —— — | | | To be completed by Clinical Coordinator after urvey is completed.) |
| 2. | Patient ID: | | | | | 8. | How was the questionnaire completed: |
| 3. | Patient code: | | | | | | Self-administered by patient/parent (1) |
| 4. | Date of visit: | | | | | | 10. |
| | | mon | | year | <u> </u> | | Interview in English (2) Interview with translator (3) |
| 5. | Visit code: | | | · | | 9. | Who was the respondent (check all that apply): |
| 6. | Form & revision: | | _1_ | _ p | 1_ | | a. Patient: (1)b. Patient's mother or female |
| 7. | Study: | | | TONIO | C <u>3</u> | | 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 le | abel here |
|---------------|-----------|
| Patient ID: | |
| Patient code: | |
| Visit code: | |

Circle one for each symptom

Degree of bother

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

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

Circle one

| | | ircie on |
|-----|--|----------|
| | I feel normal and am not tired (If this is how you feel, please circle "1" and g | |
| | to item number 17 – Thank you!) | 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 | |
| | Not as much as above | |
| 15. | Are you tired (choose only one): | |
| | When you wake up in the morning | . 1 |
| | Or does it come on with the day | |
| | Or does it have no time pattern | |
| 16. | Do you feel more tired the day after you exercise or have a lot of activity: | |
| | Yes | . 1 |

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

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

| Very good | . 1 |
|-----------|-----|
| Good | . 2 |
| Fair | . 3 |
| Poor | . 4 |
| Awful | . 5 |

18. Today's date:

Thank you for completing this questionnaire.

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

Purpose: To record archival and current laboratory test results for tests done during both screening and followup. **When**: Visits s1, f004, f012, f024, f036, f048, f060, f072, f084, f096, and f120.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat tests if archival test is not within the required time window). The window for each test is specified next to the date of blood draw. Use a calculator if you need to convert units to match the units specified on this form. Call the DCC if you have any questions about conversions or how to record a value. If is checked in item 63, the patient is not eligible for TONIC and the form should not be keyed. Attach copies of the laboratory reports to this form.

| A. Center, patient, and visit identification | C. Hematology | | |
|--|--|--|--|
| 1. Center ID: | Required at visits s1, f024, f048, f072, f096, and f120. | | |
| 2. Patient ID: | 11. Is hematology testing required at this visit: | | |
| 3. Patient code: | (Yes (No () 2) | | |
| 4. Date of visit: | 12. Date of blood draw for hematology: | | |
| day mon year | | | |
| 5. Visit code: | Date must be within the required time window; within 3 months of screening or in the time window | | |
| 6. Form & revision: | for the followup visit (check the patient's TONIC visit time window guide). | | |
| 7. Study: TONIC 3 | 13. Hemoglobin: | | |
| B. Initial screening ALT | 14. Hematocrit: | | |
| - | 14. Hematocht | | |
| 8. Is this visit s1: | 15. White blood cell count (WBC): | | |
| 11. | 10^3 cells/ μ L or 10^9 cells/L | | |
| 9. Date of blood draw for ALT (Date must be within 12 months of randomization and at least 30 days apart from the ALT done at | 16. Platelet count: | | |
| the clinic for visit s2): | cells/ μL | | |
| day mon year | | | |
| 10. Alanine aminotransferase (ALT) (<i>if ALT</i> ≤ 60 <i>U/L</i> , patient is ineligible; also, patient is ineligible if the ALT done closest in time to randomization is > 400 <i>U/L</i>): | | | |
| | | | |
| a. Upper limit of normal: | | | |
| b. Lower limit of normal: | | | |

D. Metabolic panel

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

17. Date of blood draw for metabolic panel:

| day | mon | V | ear |
|-----|-----|---|-----|

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:

| mFa/I | Ξ |
|-----------|---|

21. Bicarbonate:

| • | |
|-----------|---|
| mEq/L | _ |

22. Calcium:

| • | |
|-----------|--|
| mg/dL | |

23. Phosphate:

| • | |
|-----------|--|
| mg/dL | |

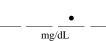
24. Blood urea nitrogen (BUN):

| 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:



27. Albumin:

| • | |
|------|--|
| g/dL | |

28. Total protein:

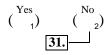


E. Fasting lipid profile

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

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

29. Is fasting lipid profile required at this visit:



30. Date of blood draw for fasting lipid profile:

| day | mon | year |
|-----|-----|------|

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

a. Triglycerides:

| mg/dL | _ |
|-------|---|
| _ | |

b. Total cholesterol:

| mg/dL | |
|-------|--|

c. HDL cholesterol level:

| | _ |
|-------|---|
| mg/dL | |

d. LDL cholesterol level:

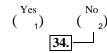
| | _ |
|-------|---|
| mg/dL | |

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:



32. Date of blood draw for fasting glucose level:



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).

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

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

| mg/dL | |
|-------|--|

G. Hepatic panel

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

34. Is hepatic panel required at this visit:

| Yes | No |
|-----------------------------------|-----------------------------------|
| $\begin{pmatrix} 1 \end{pmatrix}$ | $\begin{pmatrix} 2 \end{pmatrix}$ |
| | 41. |

35. Date of blood draw for hepatic panel:

| | · · · · · · · · · · · · · · · · · · · | |
|-----|---------------------------------------|------|
| | | |
| | | |
| day | mon | vear |

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

- **37.** Bilirubin (conjugated or direct):

| • | |
|-----------|--|
| mg/dL | |
| mg/uL | |

38. Aspartate aminotransferase (AST)

| · | U/L | |
|---|-----|--|

U/L

U/L

a. Upper limit of normal:

| b. Lower limit of normal: | | |
|----------------------------------|------|--|

39. Alanine aminotransferase (ALT)

| | U/L | |
|--|-----|--|
| | | |

a. Upper limit of normal:

| U/L | |
|-----|--|
| | |
| | |
| | |

U/L

b. Lower limit of normal: ____

| II/I | |
|------|--|

a. Upper limit of normal:

40. Alkaline phosphatase

| U/L | |
|-----|--|
| | |
| | |

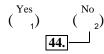
U/L

b. Lower limit of normal:

H. Vitamin B₁₂

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

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



42. Date of blood draw for vitamin B₁₂:

| _ | | = |
|-----|-----|------|
| day | mon | year |

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

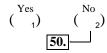
43. Vitamin B₁₂ (cobalamin) (if provided in pmol/L, multiply by 1.35 to convert to pg/ml):

| | | • | |
|-------------|-------|---|--|
| | pg/mL | | |

I. Prothrombin time, GGT, and HbA1c

Required at visits f048, f096, and f120.

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



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

| _ | | = |
|-----|-----|------|
| day | mon | vear |

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

- **47.** International normalized ratio (INR):

| | • | |
|---------------|---|---------------|
| $\overline{}$ | | $\overline{}$ |

48. Gamma glutamyl transferase (GGT):

| | U/L | |
|--|-----|--|

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) |
| No, patient is diabetic | 54. (3) |
| | 54. |

51. Date of blood draw for OGTT:

| _ | | _ |
|-----|-------|--------|
| day | mon | year |
| D | . 1 . | 1 C 11 |

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

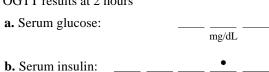
52. OGTT results at baseline

| a. Serum glucose: | $ {mg/dL}$ |
|--------------------------|------------|
| | mg/dL |

| b. Serum insulin: | • | |
|--------------------------|-------|---|
| | μU/mL | _ |

| c. Serum C peptide: | • |
|----------------------------|-------|
| 1 1 | ng/mL |

53. OGTT results at 2 hours

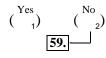


μU/mL

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:



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

| day | mon | year |
|------------------------|------------------|-------------|
| mariat la a im Ala a d | in a suin dan fa | 41 a fall a |

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

56. Free fatty acid:

| μmol/L | |
|--------|--|
| • | |

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

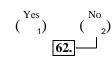
| | | • | |
|--|--|-------|--|
| | | mg/dL | |

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

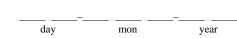
L. Pregnancy test

Required at all study visits if applicable.

59. Is pregnancy test applicable:



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

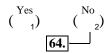


Date must be the same day as date of visit.

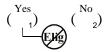
61. Pregnancy test results (*if pregnancy test is positive at s1, patient is ineligible*):

M. Eligibility check

62. Is this the s1 visit:



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



N. Administrative information

- **64.** Study Physician PIN: ____ ___
- **65.** Study Physician signature:
- **66.** Clinical Coordinator PIN: ____ ___
- **67.** Clinical Coordinator signature:
- ____
- **68.** Date form reviewed:

| day | mon | V | ear |
|-----|-----|---|-----|

LS - Laboratory Results Tests Done Only During Screening

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

When: Visit s1.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Laboratory test results may be obtained from chart review. The acceptable time interval for archival laboratory data is specified for each test and recorded next to the date of blood draw. Laboratory tests should be repeated if the blood draw date is outside the specified time interval. If is checked for any item the patient is not eligible for the TONIC trial. If is checked for an item, use caution. If the Study Physician agrees with the diagnosis, the patient is ineligible for TONIC.

| A. Center, patient, and vi | sit identification | B. Screening etiologic tests | | |
|----------------------------|--------------------|---|--|--|
| 1. Center ID: | | 8. Date of blood draw for serological assays to exclude viral causes of chronic liver | | |
| 2. Patient ID: | | disease: | | |
| 3. Patient code: | | day mon Repeat if date is greater than 1 yea screening. | year r prior to | |
| 4. Date of visit: | | a. Hepatitis B surface antigen (HBsAg) | : | |
| | | Positive | \sim $($ | |
| day | mon year | Æ | ,vig)— | |
| 5. Visit code: | <u>s 1</u> | Negative | (2) | |
| 6. Form & revision: | _1s1_ | b. Hepatitis B core total antibody (anti-HBc) (if total anti-HBc is not record results from IgG test): | available, | |
| 7. Study: | TONIC 3 | Positive | (1) | |
| 7. Study. | 101/10 | Negative | (2) | |
| | | Not available | (3) | |
| | | c. Hepatitis B surface antibody (anti-HBs): | | |
| | | Positive | $\begin{pmatrix} 1 \end{pmatrix}$ | |
| | | Negative | $\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$ | |
| | | Not available | $\begin{pmatrix} & & \\ & & \end{pmatrix}$ | |
| | | d. Hepatitis C antibody (anti-HCV) (in sult as negative if EIA is positive by negative): | | |
| | | Positive (| | |
| | | Negative | $\begin{pmatrix} & & \\ & & 2 \end{pmatrix}$ | |
| | | e. Hepatitis C virus RNA (HCV RNA): | _ | |
| | | Positive | | |
| | | Negative | (2) | |
| | | Not available | $\begin{pmatrix} & & \\ & & \end{pmatrix}$ | |

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.

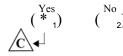
10. Antinuclear antibody (ANA):

Positive (* 1)
Negative (2)

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

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

11. Is ANA titration greater than 1:80



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

12. Antismooth muscle antibody (ASMA):

Positive (* 1)
Negative (2)

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)
Not available (3)

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

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

14. Is AMA titration greater than 1:80



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

D. Ceruloplasmin

15. Date of blood draw for ceruloplasmin:

day mon year

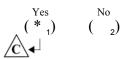
Repeat if date is greater than 10 years prior to screening.

16. Ceruloplasmin



a. Lower limit of normal: _____

b. Is ceruloplasmin below the lower limit of normal:



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

E. Alpha-1 antitrypsin

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

day mon year

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

18. Alpha-1 antitrypsin (A1AT)

mg/dL

a. Lower limit of normal:



b. A1AT deficiency (physician judgment):



TONIC

2 of 3

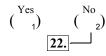
F. Iron

19. Date of blood draw for hemochromatosis screening:

day mon year

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

- **b.** Total Iron Binding Capacity: _____
- 20. Is hepatic iron index available:



21. Hepatic iron index: ______ _ __ μmol/g/year

G. Administrative information

- **22.** Study Physician PIN:
- 23. Study Physician signature:
- **24.** Clinic Coordinator PIN: ____ ___
- **25.** Clinic Coordinator signature:
- **26.** Date form reviewed:



LU - Laboratory Results - Tests Required at Visit s2

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

When: Visit s2.

Administered by: Study Physician and Clinical Coordinator.

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

| A. Center, patient, and vi | sit identificat | ion | 11. Aspartate aminotransferase (AS | ST) |
|--|------------------------------|----------------|--|-----------------------|
| 1. Center ID: | | | | |
| 2. Patient ID: | | | a. Upper limit of normal: | |
| 3. Patient code: | | | b. Lower limit of normal: | U/L |
| 4. Date of visit: | | | | U/L |
| | | | 12. Alanine aminotransferase (ALT patient is ineligible; patient is a | lso ineligible if the |
| day | mon | year | ALT done closest in time to rand U/L) | lomization is > 400 |
| 5. Visit code: | | | | T1/I |
| 6. Form & revision: | | u1_ | | U/L |
| 7. Study: | | TONIC 3 | a. Upper limit of normal: | |
| 7. Study. | | 10NIC <u>3</u> | b. Lower limit of normal: | |
| B. Hepatic panel | | | | U/L |
| This hepatic panel mu center on or after the | date when scre | ening started, | 13. Alkaline phosphatase | |
| and the ALT recorded hepatic panel (visit s | 2) must be at | least 30 days | | U/L |
| apart, but this hepatic recorded on the visit s | panel may pre s1 LR form. | e-date the ALT | a. Upper limit of normal: | |
| 8. Date of blood draw fo | r henatic nane | 1. | b. Lower limit of normal: | |
| - | r nepaute pane | | b. Lower mint of normal. | U/L |
| day | mon | year | | |
| 9. Bilirubin (total): | r | | | |
| 10. Bilirubin (conjugated | or direct): | | | |
| | | • | | |
| | | mg/dL | | |

| C. | Vitamin B ₁₂ | , free | fatty | acid, | leptin, | and |
|----|-------------------------|--------|-------|-------|---------|-----|
| | C-reactive p | rotei | n | | | |

14. Date of blood draw for vitamin B₁₂, free fatty acid, leptin, and C-reactive protein (all on serum):

| = | | _ |
|-----|-----|------|
| day | mon | year |

Date must be within 3 months of screening.

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

| | | • | |
|------|-------|---|--|
| | pg/mL | | |

16. Free fatty acid:

17. Leptin:

| μmol/L | |
|--------|--|
| • | |

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:

| =_ | | <u>_=</u> |
|-----------------------|---------------|-----------|
| day | mon | year |
| Date must be within 3 | months of scr | eening. |

- **20.** Prothrombin time (PT):
- **21.** International normalized ratio (INR):

| • | |
|------|--|
| | |

22. Gamma glutamyl transferase (GGT):

| | U/L | |
|---|-----|--|
| | • | |
| % | | |

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):

| | ${\text{mg/dL}}$ |
|----------------------------|------------------|
| b. Serum insulin: | <u>Φ</u> |
| c. Serum C peptide: | • |

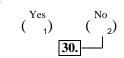
26. OGTT results at 2 hours (if 2-hour glucose ≥ 200 mg/dL, patient is ineligible)

| | mg/dL |
|--------------------------|-------|
| b. Serum insulin: | • |
| | μU/mL |

F. Pregnancy test

27. Is pregnancy test applicable:

a. Serum glucose:



ng/mL

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

at s1 or s2, patient is ineligible):

| day | mon | year |
|-----------------------|-----------------|-----------|
| Date must be the same | e day as date o | of visit. |

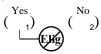
29. Pregnancy test results (if pregnancy test is positive

| Positive | (| 1) |
|----------|---|----|
| Negative | (| 2) |

23. HbA1c:

G. Eligibility check

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



H. Administrative information

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

| 32. | Study Physician signature | : |
|-----|---------------------------|---|
| | | |

| 33 | Clinical | Coordinator | PIN. | | |
|-----|-----------|-------------|-------|--|--|
| JJ. | Cililicai | Coordinator | LIII. | | |

| 34. | Clinical Coordinator signature: | |
|-----|---------------------------------|--|
| | | |

| ^ = | D . C | | |
|------------|------------|-----------|---|
| 4 | Date form | ramamad | • |
| J.J. | Date Torri | ILCVICWCU | |

| day | mon | year |
|-----|-----|------|

MA - Modifiable Activity Questionnaire

Purpose: To obtain the patient's physical activity.

When: Visits s2, f048, f096, and f120.

Administered by: Interview administered (8-12 yrs) or self-administered (13-17 yrs). Parents may assist with completion, if needed. Clinical Coordinator must be available at visits to answer questions and to review completed forms.

Respondent: Patient.

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

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

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

Modifiable Activity Questionnaire

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

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

| U, | | • | , | | | | • | • | | | | | | | | | | | Ci | iro | cle or | ne |
|----------|---------|------|-------|------|--|------|------|---|--|--|------|--|--|--|--|--|--|--|----|-----|--------|----|
| None . | | | | | | | | | | | | | | | | | | | | | . 1 | |
| 1 to 2 d | lays | | | | | | | | | | | | | | | | | | | | . 2 | |
| 3 to 5 d | lays | | | | | | | | | | | | | | | | | | | | . 3 | |
| 6 to 8 d | lays | | | | | | | | | | | | | | | | | | | | 4 | |
| 9 or mo | ore day | vs . | | | | | | | | | | | | | | | | | | | . 5 | |

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

| C | • | U, | 1 3 | , | Circle one |
|-------------|---|----|-----|---|------------|
| | | | | | Circie one |
| None | | | | | 1 |
| 1 to 2 days | | | | | 2 |
| 3 to 5 days | | | | | 3 |
| 6 to 8 days | | | | | 4 |
| | | | | | |

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

| co games, or use the computer for other activities before or after sensor. | |
|--|------------|
| | Circle one |
| None | 1 |
| 1 hour or less | 2 |
| 2 to 3 hours | 3 |
| 4 to 5 hours | 4 |
| 6 or more hours | 5 |

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

| | Circle one |
|-------------------------------------|------------|
| None | 1 |
| 1 activity | 2 |
| 2 activities | |
| 3 activities | |
| 4 or more activities | 5 |
| What activities did you compete in? | |
| | |

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

| | PAST | YEA | AR I | LEIS | SUR | RE-T | ΊM | E P | HYS | SIC | AL. | AC | ΓIV | ITY | | |
|--|---|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-----------------------|---------------------|-----------------------|
| | heck all activities that hysical education clas | | | | | | | | | | | | | | | school |
| () 04 () 07 () 10 () 13 () 16 () 19 () 22 () 25 |) 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 () 26. Wrestling () 27. Others: List each activity that you checked above in the "Activity" box below. | | | | | | | | | | | | | | | |
| | the months you did ea | | | | | | | | | | f tim | e spe | ent in | each acti | vity. | |
| Activity Code # | Activity | J A N | F E B | M A R | A P R | M A Y | J U N | J U L | A U G | S E P | O C T | N O V | D E C | Months per Year | Days per Week | Minutes per Day |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | |

17. Today's date:

PE - Physical Examination

Purpose: Record detailed physical exam findings.

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

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

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

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

| A. Center, patient, and visi | t identification | 9. Weight (shoes off) | |
|------------------------------|------------------|--|---|
| 1. Center ID: | | a. Weight, 1st measurement: | • |
| 2. Patient ID: | | b. Weight, 2nd measurement: | |
| 3. Patient code: | | c. Units: | |
| 4. Visit date: | | Pounds Kilograms | $\begin{pmatrix} & & & \\ & & & \\ & & & \end{pmatrix}$ |
| | mon year | 10. Waist (standing, at midpoint betw | veen highest point |
| 5. Visit code: | | of iliac crest and lowest part of repeat waist measurements un measurements within 4 in (10.2 of | til you have two |
| 6. Form & revision: | _pe1_ | a. Circumference, 1st measurem | nent: |
| 7. Study: | TONIC_3_ | b. Circumference, 2nd measurer | circumference ment: |
| B. Measurements | | waist c | circumference |
| 8. Height (shoes off) | | c. Units: Inches | (1) |
| a. 1st measurement: | • | Centimeters | $\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$ |
| b. 2nd measurement: | - — — — — • | | |
| c. Units: | | | |
| Inches | (1) | | |
| Centimeters | (_) | | |

| 11. Hip (standing, at fullest part of the hips; repeat hip measurements until you have two measurements within 4 in (10.2 cm) of each other) | | | 16. Respiratory rate: | | | | |
|---|--|--|--|----|--------|--|--|
| | a. Circumference, 1st measurem | nent: | C. Examination findings | | | | |
| | hin c | rcumference | 17. Skin: | | | | |
| | b. Circumference, 2nd measurer | | Normal | (| 1) | | |
| | hip ci | rcumference | [20.]- Abnormal | (| , , | | |
| | c. Units: | | Abhormai | (| 2) | | |
| | Inches | (1) | 18. Acanthosis nigricans (check only one): | | | | |
| | Centimeters | $\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$ | Absent (not detectable on close inspection) | (| 0 | | |
| 12. | Triceps (right arm, with elbow or relaxed; repeat skin fold measu have two within 10 mm of edmid-upper arm circumference u | rements until you ch other; repeat | Present (clearly present on close inspection, not visible to casual observer, extent not measurable) | (| 1) | | |
| | within 1.5 in (3.8 cm) of each of a. Skin fold, 1st measurement: | her) | Mild (limited to base of skull, not extending to lateral margins of neck, < 3 inches in breadth) | (| 2) | | |
| | b. Skin fold, 2nd measurement: | | Moderate (extending to lateral margins of neck, 3-6 inches in breadth, not visible from patient's front) | (| 3) | | |
| | | | Severe (extending anteriorly, > 6 inches in breadth, visible from front) | (| 4) | | |
| | c. Mid-upper arm circumference measurement: | • | 19. Other skin abnormality (check all that apply | y) | | | |
| | | m circumference | a. Jaundice: | (| 1) | | |
| | d. Mid-upper arm circumference measurement: | e, 2nd | b. Palmar erythema: | (| ,) | | |
| | | • | c. Spider angiomata: | (|) | | |
| | e. Units for arm circumference: | m circumference | | (| 1/ | | |
| | Inches | () | d. Other (specify): | (| 1) | | |
| | Centimeters | $\begin{pmatrix} & 1 \\ & 2 \end{pmatrix}$ | | | | | |
| 12 | Tommoreture (Ougl) | | e. None of the above: | (| 1) | | |
| 13. | Temperature (Oral) | • | 20. Head, eyes, ears, nose, throat: | | | | |
| | a. Degrees: | <u> </u> | Normal | (| 1) | | |
| | b. Scale: | | 22. | | J | | |
| | Fahrenheit | () | Abnormal | (| 2) | | |
| | Centigrade | (₁) | 21. Abnormality of the head, eyes, nose, | | | | |
| 14. | Blood pressure | (2/ | throat (check all that apply) | | | | |
| | 1 | | a. Jaundice: | (| ,) | | |
| | a. Systolic: | mmHg | b. Other (specify): | (| 1) | | |
| | h Diagtalia. | , and the second | | | | | |
| | b. Diastolic: | mmHg | specify | | | | |
| 15 | Resting radial pulse: | | | | | | |
| 13. | Results radial pulse. | beats/minute | | | | | |

22. Neck:

Normal (1)
Abnormal (2)

specify abnormality

23. Lymphatic:

Normal (1

Abnormal (2

specify abnormality

24. Chest and lungs:

Normal
Abnormal
specify

25. Heart:

Normal

Abnormal

specify abnormality

26. Abdomen:

Normal (1)
Abnormal (28.

27. Abdomen abnormality (check all that apply)

a. Ascites: (1) **b.** Obese: (1) **c.** Other (specify): (1)

c. Other (specify):

specify

28. Liver and spleen:

Normal (

30. — (

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

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

b. Splenomegaly:

c. Other (specify):

specify

specify

30. Extremities:

Not performed

(0)

32.

Normal

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:

e. Other (specify):

specify

32. Genitourinary/pelvis:

Not performed

(0)

Normal

Abnormal

(1)

specify

33. Nervous system:

Not performed

(0)

Normal

(1)

Abnormal

| 34. | Abnormality of the nervous system (check all that apply): | | | | Female Tanner Staging | | | |
|--|--|------|----------|---|--|--------------|--|--|
| | a. Mental status abnormal: | (| 1) | 40. | Breast stage: | | | |
| | b. Asterixis: | (| 1) | | | 1-5 | | |
| | c. Other (specify): | (| 1) | 41. | Pubic hair stage: | 1-5 | | |
| | specify | | | 42. | Has menarche occurred: | (Yes (No 2) | | |
| D. T | anner Staging | | | | | | | |
| 35. | Is Tanner staging required for this participant (Note: Required at screening visit.) (check only one): | | | 43. | What was the participant's age menarche: | age in years | | |
| Yes, participant has not reached full sexual maturity or is 17 years old or younger: 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) | | | E. A | E. Ability to swallow study medication (At the randomization visit the Study Phenoian/Clinical Coordinator will be asked to prosessurance that the patient is able to swallow TONIC study medication; if needed, you could the patient to swallow a capsule from the place metformin provided by the DCC). | | | | |
| | 44 | 4. — | | 44. | Was the patient able to swallow placebo metformin capsule (ch | | | |
| 36. | Is the patient female: Yes (1) 40. | (| No 2) | | Yes, patient was able to swallo No, patient was unable to swal capsule | * '' | | |
| | Male Tanner Staging | | | | Did not ask for a demonstratio | n at this | | |
| 37. | Genital stage: | _ | 1-5 | | time | (3) | | |
| | | | | F. A | Administrative information | | | |
| 38. | Testicular volume (smallest of right and left): | cc | | 45. | Study Physician PIN: | | | |
| 39. | Pubic hair stage: | | 1-5 | 46. | Study Physician signature: | | | |
| | 44 | 4.]— | J | 47. | Clinical Coordinator PIN: | | | |
| | | | | 48. | Clinical Coordinator signature | : | | |
| | | | | 49. | Date form reviewed: | vear | | |

PF - Focused Physical Examination

Purpose: Record focused physical exam findings.

When: Visits f004, f012, f024, f036, f060, f072, and f084. Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

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

| A. Center, patient, and visi | it identific | cation | 10. Waist (standing, at midpoint b | |
|--|--------------|-------------|---|--|
| 1. Center ID: | | | of iliac crest and lowest par repeat waist measurements measurements within 4 in (10. | until you have two |
| 2. Patient ID: | | | a. 1st measurement: | |
| 3. Patient code: | _ | | b. 2nd measurement: | |
| 4. Visit date: | | | | <u> </u> |
| | | | c. Units: | () |
| day | mon | year | Inches Centimeters | $\begin{pmatrix} & & 1 \\ & & 2 \end{pmatrix}$ |
| 5. Visit code:6. Form & revision: | | pf1_ | 11. Hip (standing, at fullest part of measurements until you have within 4 in (10.2 cm) of each | e two measurements |
| 0. Politi & Tevision. | _ | <u> </u> | a. 1st measurement: | oner |
| 7. Study: | | TONIC 3 | a. 1st measurement: | • |
| B. Measurements | | | b. 2nd measurement: | • |
| 8. Height (shoes off) | | | c. Units: | |
| a. 1st measurement: | | | Inches | (1) |
| | | <u> </u> | Centimeters | (2) |
| b. 2nd measurement: | | • | 12. Temperature (<i>oral</i>) | |
| c. Units: | | | a. Degrees: | <u> </u> |
| Inches | | (1) | | |
| Centimeters | | (2) | b. Scale: | |
| 9. Weight (shoes off) | | . 2 | Fahrenheit: Centigrade: | (1) |
| | | | Configuac. | (2) |
| a. 1st measurement: | | • | 13. Blood pressure | |
| b. 2nd measurement: | | • | a. Systolic: | mmHg |
| c. Units: | | | b. Diastolic: | |
| Pounds | | (,) | | mmHg |
| Kilograms | | () | | |

year

| 14. Resting radial pulse: | | D. Administrative information |
|--|----------------------|---------------------------------------|
| 14. Resulig radial pulse. | beats/minute | D. Administrative miorination |
| 15. Respiratory rate: | | 18. Study Physician ID: |
| 13. Respiratory rate. | breaths/minute | 10. Study Physician signature. |
| C. Liver signs | | 19. Study Physician signature: |
| 16. Liver and spleen: | | |
| Normal | (1) | 20. Clinical Coordinator ID: |
| Abnormal | 18. (₂) | 21. Clinical Coordinator signature: |
| 17. Abnormality (check all that apply) | | |
| a. Ascites: | (1) | _ |
| b. Asterixis: | (1) | 22. Date form reviewed: |
| c. Contractures: | (1) | |
| d. Hepatomegaly: | (1) | day mon |
| If Yes, span from right midclavi | cular line: | |
| | | |
| e. Jaundice: | cm (₁) | |
| f. Muscle wasting: | (1) | |
| g. Palmar erythema: | (₁) | |
| h. Pedal edema: | | |
| | (1) | |
| i. Spider angiomata: | (1) | |
| j. Splenomegaly: | (1) | |
| k. Other, (specify): | (1) | |

specify abnormality

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 (m) is checked for any item, the patient is not eligible for TONIC and the form should not be keyed.

| A. | Center, | patient | and | visit | iden | tifica | tion |
|----|---------|---------|-----|-------|------|--------|------|
|----|---------|---------|-----|-------|------|--------|------|

- 1. Center ID:
- 2. Patient ID:
- **3.** Patient code:
- **4.** Visit date:

| = | | = |
|-----|-----|------|
| day | mon | year |

- **5.** Visit code:
- 6. Form & revision: <u>r g 1</u>
- 7. Study:

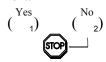
TONIC 3

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:



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

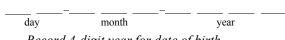


10. Has the patient signed the TONIC informed assent statement:

| Yes | (1 |
|-------------------------------------|--------|
| No | (2 |
| | STOP — |
| Not using assent | (3 |
| Not using assent for this age child | (. |

C. Information about patient

11. Date of birth:



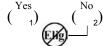
Record 4-digit year for date of birth.

12. Age at last birthday:



years

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



14. Gender:

Male Female

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

Hispanic or Latino or Latina Not Hispanic, not Latino, not Latina

| 10. | Latino, or Latina origin best (s h o w t tient/guardian Flash Card #1 and ask the | stepmother, or other) (show patient/guardi Flash Card #4; check only one): | | | | | |
|-----|---|---|----------------|---|--------|----------------|--|
| | dent to pick the subcategory that best desc patient's Hispanic, Latino, or Latina orig only one): | | | Not applicable (mother is deceased or patient has no stepmother or female guardian) | (| 0 | |
| | Mexican | (| 1) | 19 or younger | (| 1) | |
| | Puerto Rican | (| 2) | 20-29 years | (| 2) | |
| | Cuban | (| 3) | 30-39 years | (| 3) | |
| | South or Central American | (| 4) | 40-49 years | (| 4) | |
| | Other Spanish culture or origin | (| ₅) | 50-59 years | (| ₅) | |
| | | | | 60 years or older | (| 6) | |
| | specify | | | • | (| 6) | |
| 17. | Racial category (show the patient/guardi Card #2 and ask the respondent to pick gory or categories that describe the pati check all that apply) | the co | ate- | 21. Highest educational level achieved by patient's female guardian (mother, stepn other) (show patient/guardian Flash Coeducation of female guardian is unknown as "n"; check only one): | ard #5 | 5; if | |
| | a. American Indian or Alaska Native: | (| 1) | Never attended school | (| 0 | |
| | b. Asian: | (| 1) | Did not complete high school | (| 1) | |
| | c. Black, African American, Negro, or | | | Completed high school | (| 2) | |
| | Haitian: | (| 1) | Some college or post high school | (| ` | |
| | d. Native Hawaiian or other Pacific | | | education or training | (| 3) | |
| | Islander: | (| 1) | Bachelor's degree or higher | (| 4) | |
| | e. White:f. Patient refused: | (| 1) 1) | 22. Current age of patient's male guardian (stepfather, or other) (show patient/g Flash Card #4; check only one): | | | |
| 18. | In what country was the patient born (ch one): | eck d | only | Not applicable (father is deceased or patient has no stepfather or male | (| ` | |
| | Continental US (includes Alaska) or | | | guardian) | (| 0) | |
| | Hawaii | (| 1) | 19 or younger | (| 1) | |
| | Other, (specify): | (| 2) | 20-29 years | (| 2) | |
| | | | | 30-39 years | (| 3) | |
| | specify | | | 40-49 years | (| 4) | |
| | | | | 50-59 years | (| 5) | |
| 19. | Patient's current grade level in school (or home school) (show the patient/guardic Card #3 and ask the respondent to pick gory that describes the patient best; if | an Fl the co | ate- mer | 60 years or older23. Highest educational level achieved by patient's male guardian (father, stepform) | | | |
| | time, report grade entering in the fall; chone): Grades 1 to 5 | <i>1еск с</i> (| ` | other) (show patient/guardian Flash Control education of male guardian is unknown, "n"; check only one): | | | |
| | Grades 6-8 | (| 1) | Never attended school | (| 0 | |
| | Grades 9-12 | (| ₂) | Did not complete high school | Ì | 1) | |
| | Grades 7-12 | (| 3) | Completed high school | ì | 2) | |
| | | | | Some college or post high school | (| 2) | |
| | | | | education or training | (| 3) | |
| | | | | Bachelor's degree or higher | (| 4) | |
| | | | | | | | |

| Patient 1 | D. | | |
|-----------|----|--|--|

| 24. (| Combined annual income before taxes of |
|-------|---|
| | ll members of patient's household (show guard- |
| | an Flash Card #6 and ask respondent to pick the |
| | category that describes the patient's combined |
| P. | nousehold 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 | (| (80 |
| Pediatric weight disorders clinic | (| (90 |
| 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:

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

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 <i>tient code in item 3):</i> | (record | pa |
|-----|---|---------|----|
| | | | |
| | | 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.

|--|

G. Administrative information

- **31.** Clinical Coordinator PIN:
- **32.** Clinical Coordinator signature:
- 33. Date form reviewed:

 day mon year