TONIC

AD – Alcohol Use Disorders Identification Test (AUDIT)

Purpose: To screen for current heavy drinking and/or active alcohol abuse or dependence.
When: Visit s1.
Administered by: Self-administered *(age 13 or older)*, interviewer administered *(age 8-12)*. Clinical Coordinator must be available at visits to answer questions and review completed forms.
Respondent: Patient, age 8 or older. Patients age 13 or older should complete the form without help from family. Clinical Coordinator/parent can assist patients age 8-12.
Instructions: Flash Card #11, Drink Equivalents, may be used with this form. The Clinical Coordinator should complete section A below and write the patient ID on pages 2-3. If the form is self-administered by the patient, the patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-3. The Clinical Coordinator should review the completed form for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be reattached to pages 2-3 and the Clinical Coordinator then should complete section B below.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

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

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

7. Study: TONIC 3

B. Administrative information

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

8. How was the questionnaire completed:

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

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

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

_____
specify

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

_____

11. Date form reviewed:

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

AD – Alcohol Use Disorders Identification Test (AUDIT)

Instructions: This survey asks for your views about your alcohol use. Please check one for each question below *(items 1-11 are for clinical center use only)* .

12. How often do you have a drink containing alcohol?

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

→ **22.**

13. How many drinks containing alcohol do you have on a typical day when you are drinking?

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

14. How often do you have six or more drinks on one occasion?

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

15. How often during the last year have you found that you were not able to stop drinking once you had started?

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

16. How often during the last year have you failed to do what was normally expected from you because of drinking?

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

17. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

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

18. How often during the last year have you had a feeling of guilt or remorse after drinking?

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

19. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

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

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

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

21. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

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

22. Today's date:

_____

Thank you for completing this questionnaire.

TONIC

BG - Baseline History

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

A. Center, visit, and patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: s 1 ____ ____

6. Form & revision: b g 2

7. Study: TONIC 3

B. Family history

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

Yes (1) No (2)
10.

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

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

_____
specify

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

Yes (1) No (2)
12.

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

Yes (1) No (2)

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

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

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

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

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

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

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

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

C. NAFLD history

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

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

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

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

_____
specify

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

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

_____
specify

D. Weight history

19. What was the patient's birthweight:

____ ____–____ ____
lbs oz

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

____ ____ ____
lbs

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

____ ____ ____
lbs

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

____ ____
age in years

E. Tobacco cigarette smoking history

(interview with patient; not by chart review)

23. Have you ever smoked tobacco cigarettes:

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

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

Yes (1) No (2)

28. ⌊

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

____ ____
years

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

____ ____
years

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

____ ____ ____
cigarettes/day

F. Menstrual history

28. Is the patient female:

(Yes 1) (No 2)

31.

29. Menarche history

a. Has menarche occurred:

(Yes 1) (No 2)

31.

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

____ ____
age in years

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

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

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

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

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

o. Other gastrointestinal bleeding: (1)

p. Biliary diversion: (1)
C

q. Metabolic acidosis: (1)
C

r. Ascites: (1)
C

s. Edema: (1)

t. Hepatic encephalopathy: (1)
C

u. Portal hypertension: (1)
C

v. Hepatorenal syndrome: (1)
C

w. Hepatopulmonary syndrome: (1)
C

x. Short bowel syndrome: (1)
C

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

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

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

ab. Hepatocellular carcinoma: (1)
C

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

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

ae. Peripheral neuropathy: (1)

af. Seizure disorder or epilepsy: (1)

ag. Drug allergies: (1)

ah. Hypothyroidism: (1)

ai. Hypertension: (1)

aj. Cerebrovascular disease: (1)

ak. Dysbetalipoproteinemia: (1)
C

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

am. Pancreatitis: (1)

an. Cholelithiasis: (1)
C

ao. Coronary artery disease: (1)
C

ap. Congestive heart failure: (1)
C

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

ar. Kidney disease: (1)
C

as. Polycystic ovary syndrome: (1)

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

au. Dermatologic disorders: (1)

av. Myopathy: (1)

aw. Myositis: (1)

ax. Major depression: (1)

ay. Schizophrenia: (1)

az. Bipolar disorder: (1)

ba. Obsessive compulsive disorder: (1)

bb. Severe anxiety or personality disorder: (1)

bc. Substance abuse: (1)
C

bd. None of the above: (1)

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

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

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

c. Biliopancreatic diversion: (1)
C

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

_____

e. None of the above: (1)

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

Yes (1) → Elig No (2)

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

Yes (1) → Elig No (2)

35. Organ, limb, or bone marrow transplant

a. Has the patient ever received a liver transplant:

Yes (1) → Elig No (2)

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

Yes (1) No (2)

H. Drugs historically associated with NAFLD

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

a. Acetylsalicylic acid (ASA): (1)

b. Aspirin - 325 mg: (1)

c. Demeclocycline (Declomycin): (1)

d. Divalproex (Depakote): (1)

e. Doxycycline (Monodox): (1)

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

g. Oxytetracycline (Terramycin): (1)

h. Tetracycline (Achromycin): (1)

i. Valproate sodium (Depacon): (1)

j. Valproic acid (Depakene): (1)

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

_____

l. None of the above: (1)

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

Yes (*1) → C No (2)

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

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

a. Betamethasone sodium (Celestone): (1)

b. Cortisol: (1)

c. Cortisone: (1)

d. Dexamethasone (Decadron): (1)

e. Hydrocortisone (Hydrocortone): (1)

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

g. Prednisolone (Prelone): (1)

h. Prednisone: (1)

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

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

_____

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

_____

l. None of the above: (1)

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

Yes (*1) → C No (2)

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

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

a. Boldenone undecylenate (Equipoise): (1)

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

c. Methandrostenolone (Dianabol): (1)

d. Methyltestosterone (Android): (1)

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

f. Oxandrolone (Oxandrin): (1)

g. Oxymetholone (Anadrol): (1)

h. Stanzolol (Winstrol): (1)

i. Tamoxifen (Nolvadex): (1)

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

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

_____

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

_____

m. None of the above: (1)

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

Yes (*1) → C No (2)

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

I. Use of antidiabetic drugs

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

Yes (1) → Elig No (2)

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

a. Acarbose (Precose): (1)

b. Acetohexamide (Dymelor): (1)

c. Chlorpropamide (Diabinese): (1)

d. Glimepiride (Amaryl): (1)

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

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

g. Insulin: (1)

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

i. Miglitol (Glycet): (1)

j. Nateglinide (Starlix): (1)

k. Pioglitazone (Actos): (1)

l. Repaglinide (Prandin): (1)

m. Rosiglitazone (Avandia): (1)

n. Tolazamide (Tolinase): (1)

o. Tolbutamide (Orinase): (1)

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

_____

q. None of the above: (1)

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

Yes (*1) → C No (2)

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

J. Use of antiNAFLD drugs and vitamins

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

a. Betaine (Cystadone): (1)

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

c. Metformin: (1)

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

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

f. Milk thistle: (1)

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

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

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

_____
specify

j. None of the above: (1)

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

Yes (*1) → C No (2)

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

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

Yes (1) No (2)

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

Yes (1) No (2) → 50.

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

Yes (*1) → C No (2)

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

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

Yes (1) → Elig No (*2)

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

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

Yes (1) → Elig No (2)

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

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

b. Vitamin C: (1)

c. Vitamin D: (1)

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

_____

e. None of the above: (1)

K. Use of statins, fibrates, and antiobesity drugs

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

a. Atorvastatin (Lipitor): (1)

b. Colestipol hydrochloride (Colestid): (1)

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

d. Fenofibrate (Tricor): (1)

e. Fluvastatin sodium (Lescol): (1)

f. Lovastatin (Mevacor): (1)

g. Nicotinic acid (Niaspan): (1)

h. Pravastatin sodium (Pravachol): (1)

i. Rosuvastatin (Crestor): (1)

j. Simvastatin (Zocor): (1)

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

_____

l. None of the above: (1)

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

a. Dexfenfluramine hydrochloride (Redux): (1)

b. Fenfluramine hydrochloride (Pondimin): (1)

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

d. Orlistat (Xenical): (1)

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

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

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

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

_____

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

_____

j. None of the above: (1)

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

Yes (*1) No (2)

C

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

L. Use of other medications and supplements

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

a. Acetaminophen (Tylenol): (1)

b. Aspirin - 325 mg: (1)

c. Celecoxib (Celebrex): (1)

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

e. Indomethacin (Indocin): (1)

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

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

_____

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

_____

i. None of the above: (1)

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

a. Cimetidine (Tagamet): (1)

b. Esomeprazole magnesium (Nexium): (1)

c. Famotidine (Pepcid): (1)

d. Lansoprazole (Prevacid): (1)

e. Nizatidine (Axid): (1)

f. Omeprazole (Prilosec): (1)

g. Ranitidine (Zantac): (1)

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

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

_____

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

_____

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

_____

l. None of the above: (1)

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

a. Albuterol: (1)

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

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

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

e. Loratadine (Claritin): (1)

f. Mometasone furoate (Nasonex): (1)

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

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

_____

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

_____

j. None of the above: (1)

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

a. Alpha-lipoic acid: (1)

b. Beta-carotene: (1)

c. Calcium (any form): (1)

d. Carnitine (any form): (1)

e. Chondroitin (any form): (1)

f. Cod liver oil: (1)

g. Coenzyme Q: (1)

h. Dichloroacetate: (1)

i. Echinacea: (1)

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

k. Flax seed oil: (1)

l. Garlic: (1)

m. Ginkgo biloba: (1)

n. Glucosamine (any form): (1)

o. Lecithin: (1)

p. Magnesium: (1)

q. N-acetyl-cysteine: (1)

r. Potassium (any form): (1)

s. Saw palmetto: (1)

t. Selenium: (1)

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

v. Taurine: (1)

w. Zinc picolinate: (1)

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

_____

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

_____

z. None of the above: (1)

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

a. Isotretinoin (Accutane): (1)

b. Levonorgestrel (Norplant): (1)

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

d. Liothyronine (Cytomel): (1)

e. Oral contraceptives: (1)

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

g. Trientine hydrochloride (Syprine): (1)

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

_____

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

_____

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

_____

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

_____

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

_____

m. None of the above: (1)

M. Willingness to use effective birth control methods

61. Are you female and of childbearing potential:

Yes (1) No (2)

65.

62. Are you currently pregnant:

Yes (1) No (2)

Elig

63. Are you currently breast feeding:

Yes (* 1) No (2)

C

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

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

Yes (1) No (2)

Elig

N. Administrative information

65. Study Physician PIN: ____ ____ ____

66. Study Physician signature:

_____

67. Clinical Coordinator PIN: ____ ____ ____

68. Clinical Coordinator signature:

_____

69. Date form reviewed:

____ ____–____ ____ ____–____ ____

day mon year

Central Histology Review

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

A. Clinic, patient and visit identification

__ __ __ __ 1. Center ID

__ __ __ __ 2. Patient ID

__ __ __ 3. Patient code

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

__ __ __ __ 5. Visit code

c r 1 6. Form and revision

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

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

B. Slide sequence number

9. Sequence number for

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

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

__ __ . . . c. Iron stained slide

__ __ . . . d. Other slide

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

C. Administrative information

__ __ __ 10. CC Initials

_____ 11. CC Signature

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

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

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

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

_____ 15. Biopsy length (mm)

H & E stain

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

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

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

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

17. Inflammation

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

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

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

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

18. Liver cell injury

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

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

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

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

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

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

Masson's trichrome stain

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

22. Iron stain

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

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

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

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

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

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

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

26. Features suggestive of steatohepatitis etiology for cryptogenic cirrhosis:

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

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

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

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

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

27. Other comments: _____

TONIC

DR - Death Report

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: n ____ ____ ____

6. Form & revision: d r 1

7. Study: TONIC_3

B. Death information

8. Date of death:

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

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

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

_____
other source

_____
other source

10. Place of death:

_____
city/state/country

_____
city/state/country

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

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

_____
specify

_____
specify

Unknown (6)

C. Administrative information

12. Study Physician PIN: ____ ____ ____

13. Study Physician signature:

_____

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

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

TONIC

DX - DEXA Scan for Body Fat

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: d x 1

7. Study: TONIC 3

B. DEXA scan information

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

(Yes 1) (No 2)

10.

9. Specify why DEXA scan was not performed

a. Patient is too heavy: (1)

b. Scanner is broken: (1)

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

_____
specify

14.

10. DEXA scanner used:

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

_____
specify make & model

C. DEXA results summary

11. Date of DEXA scan:

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

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

____ ____ • ____ ____
%

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

____ ____ • ____ ____
%

C. Administrative information

14. Clinical Coordinator PIN: ____ ____ ____

15. Clinical Coordinator signature:

_____

16. Date form reviewed:

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

TONIC

HI - Followup Medical History

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

A. Center, visit, and patient identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: h i 1

7. Study: TONIC 3

B. Interval identification

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

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

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

____ ____ ____ ____

C. NAFLD evaluation

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

(* Yes 1) (No 2)

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

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

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

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

14. ____

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

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

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

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

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

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

(Yes 1) (No 2)

17. ⌊

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

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

____ ____ ____ # cigarettes per day

F. Medical history

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

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

ax. Major depression: (1)

ay. Schizophrenia: (1)

az. Bipolar disorder: (1)

ba. Obsessive compulsive disorder: (1)

bb. Severe anxiety or personality disorder: (1)

bc. Substance abuse: (1)

bd. None of the above: (1)

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

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

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

c. Biliopancreatic diversion: (1)

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

_____

e. None of the above: (1)

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

(Yes 1) (No 2)

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

(Yes 1) (No 2)

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

(Yes 1) (No 2)

22. ____

If Yes, specify reason:

_____
specify

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

(Yes 1) (No 2)

23. ____

If Yes, specify:

_____
specify

G. Medication use

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

a. Acarbose (Precose): (1)

b. Acetohexamide (Dymelor): (1)

c. Chlorpropamide (Diabinese): (1)

d. Glimepiride (Amaryl): (1)

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

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

g. Insulin: (1)

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

i. Miglitol (Glycet): (1)

j. Nateglinide (Starlix): (1)

k. Pioglitazone (Actos): (1)

l. Repaglinide (Prandin): (1)

m. Rosiglitazone (Avandia): (1)

n. Tolazamide (Tolinase): (1)

o. Tolbutamide (Orinase): (1)

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

_____

q. None of the above: (1)

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

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

_____

m. None of the above: (1)

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

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

_____

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

_____

j. None of the above: (1)

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

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

_____

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

_____

j. None of the above: (1)

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

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

_____

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

_____

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

_____

l. None of the above: (1)

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

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

_____

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

_____

l. None of the above: (1)

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

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

_____

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

_____

m. None of the above: (1)

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

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

_____

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

_____

j. None of the above: (1)

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

Yes (1) No (2)

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

Yes (1) No (2)

35. ____

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

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

_____

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

Yes (*1) No (2)

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

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

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

_____

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

_____

ae. None of the above: (1)

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

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

_____

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

_____

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

_____

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

_____

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

_____

x. None of the above: (1)

H. Administrative information

37. Study Physician PIN: ____ ____ ____

38. Study Physician signature:

_____

39. Clinical Coordinator PIN: ____ ____ ____

40. Clinical Coordinator signature:

_____

41. Date form reviewed:

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

TONIC

IE - Interim Event Report

Purpose: To document (1) events that occur after registration but before randomization, or between regular followup visits that impact on the patient's treatment or participation in TONIC (eg, temporary or permanent cessation of study medication), or (2) adverse events associated with study drug that do not meet the criteria for Serious Adverse Event/IND Safety Report (AN) form, or participation in TONIC, or (3) other event that clinical center staff feel should be reported now rather than wait until the next followup visit and that is not recorded on another TONIC form. Adverse events associated with TONIC study drugs that are both serious and unexpected should not be reported on this (IE) form, but should be recorded on the AN form.

When: As needed; use visit code n. If more than one event is reported on the same calendar day (ie, same date in item 4 for all events), use visit code n for first event, n1 for second event, etc.

Administered by: Study Physician and Clinical Coordinator.

Instructions: Complete and key this form for any event that meets the criteria above. The short name (item 21) and the severity code (item 22) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.nashcrn.com. Click on Documents and then click on General Documents. Fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher (Fax 410-955-0932).

NASH CRN Data Coordinating Center telephone number: (410) 955-8175.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of report:

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

5. Visit code: n ____ ____ ____

6. Form & revision: i e 1

7. Study: TONIC 3

B. Visit interval identification

8. Most recently completed visit (screening or followup)

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

b. Visit code: ____ ____ ____ ____

C. Patient information

9. Date randomized in TONIC *(enter n if patient is not yet randomized):*

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

10. Gender:

Male (1)
Female (2)

11. Age at time of event: ____ ____
years

12. Is the patient currently receiving the metformin-series study drug:

Yes (1) No (2)

13. Is the patient currently receiving the vitamin E-series study drug:

Yes (1) No (2)

14. Summarize the patient's history of treatment with TONIC study drugs *(eg, how long has patient been on study drugs, have there been any treatment interruptions):*

D. Event description

15. Is the event associated with TONIC study drugs:

Yes (1) No (2)

18.

16. Is the event due to the metformin-series study drug:

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

17. Is the event due to the vitamin E-series study drug:

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

18. Date event started:

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

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

a. Drug dispensing mixup:	(1)
b. Medication related event:	(1)
c. Study procedure related event:	(1)
d. Drug interactions:	(1)
e. Worsening of a co-morbid illness:	(1)
f. Patient reported symptom of hepatotoxicity:	(1)
g. Hypoglycemia:	(1)
h. New-onset diabetes:	(1)
i. Pregnancy *(patient):*	(*1)
j. Intravenous contrast dye use:	(1)
k. General anesthesia:	(1)
l. Lactic acidosis:	(1)
m. Other *(specify):*	(1)

_____

_____

**TONIC study drugs will be discontinued if the patient herself is pregnant. Contact the NASH CRN Data Coordinating Center to unmask the study drugs. Complete a Study Drug Dispensing and Return (RD) Form.*

20. Describe event:

_____

_____

_____

_____

_____

_____

21. Short name for event if applicable *(short names for AEs are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents):*

Not applicable (0)

_____

_____

22. Severity grade *(severity grades are listed in the CTCAE v3.0 document available at www.nashcrn.com; click on Documents and then click on General Documents; use Serious Adverse Event Report (AN) to report serious and unexpected adverse events or call the DCC if unsure what to do):*

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

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

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

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

24. What action was taken:

_____

_____

_____

_____

_____

_____

25. Other comments on event:

_____

_____

_____

_____

_____

_____

E. Administrative information

26. Clinical Coordinator PIN: ____ ____ ____

27. Clinical Coordinator signature:

_____

28. Study Physician PIN: ____ ____ ____

29. Study Physician signature:

_____

30. Date form reviewed:

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

Key this form and fax the DCC (Attention: Aynur Ünalp-Arida) a copy of this form if severity grade is 3 or higher. We are asking for copies of these reports on serious events so that we assure appropriate and timely study wide review. The received reports will be reviewed by Jeanne Clark, the Safety Officer, for appropriate further review by the Steering Committee and Data and Safety Monitoring Board.

TONIC

LP – Symptoms of Liver Disease (Children)

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

A. Center, patient, and visit identification

1. Center ID: _____ _____ _____ _____

2. Patient ID: _____ _____ _____ _____

3. Patient code: _____ _____ _____

4. Date of visit:

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

5. Visit code: _____ _____ _____ _____

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

7. Study: TONIC 3

B. Administrative information

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

8. How was the questionnaire completed:

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

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

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

_____
specify

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

_____

11. Date form reviewed:

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

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

Symptoms of Liver Disease

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

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

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

Circle one for each symptom

Degree of bother

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

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

Circle one for each symptom

Degree of bother

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

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

Circle one

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

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

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

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

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

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

Yes 1
No 2

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

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

Very good 1
Good 2
Fair 3
Poor 4
Awful 5

18. Today's date:

_____

Thank you for completing this questionnaire.

TONIC

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

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: l r 1

7. Study: TONIC 3

B. Initial screening ALT

8. Is this visit s1:

( ) Yes (1) ( ) No (2) → **11.**

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

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

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

____ ____ ____
U/L

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

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

C. Hematology

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

11. Is hematology testing required at this visit:

( ) Yes (1) ( ) No (2) → **17.**

12. Date of blood draw for hematology:

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

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

13. Hemoglobin: ____ ____ • ____
g/dL

14. Hematocrit: ____ ____ • ____
%

15. White blood cell count (WBC):

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

16. Platelet count:

____ ____ ____, ____ ____ ____
cells/ µL

D. Metabolic panel

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

17. Date of blood draw for metabolic panel:

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

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

18. Sodium: ____ ____ ____ mEq/L

19. Potassium: ____ ____ • ____ mEq/L

20. Chloride: ____ ____ ____ mEq/L

21. Bicarbonate: ____ ____ • ____ mEq/L

22. Calcium: ____ ____ • ____ mg/dL

23. Phosphate: ____ ____ • ____ mg/dL

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

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

____ ____ • ____ mg/dL

26. Uric acid: ____ ____ • ____ mg/dL

27. Albumin: ____ • ____ g/dL

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

E. Fasting lipid profile

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

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

29. Is fasting lipid profile required at this visit:

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

31. ⌊

30. Date of blood draw for fasting lipid profile:

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

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

a. Triglycerides: ____ ____ ____ mg/dL

b. Total cholesterol: ____ ____ ____ mg/dL

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

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

F. Fasting glucose

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

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

31. Is fasting glucose required at this visit:

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

34. ⌊

32. Date of blood draw for fasting glucose level:

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

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

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

____ ____ ____
mg/dL

G. Hepatic panel

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

34. Is hepatic panel required at this visit:

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

41.

35. Date of blood draw for hepatic panel:

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

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

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

37. Bilirubin (conjugated or direct):

____ ____ • ____
mg/dL

38. Aspartate aminotransferase (AST)

____ ____ ____
U/L

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

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

39. Alanine aminotransferase (ALT)

____ ____ ____
U/L

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

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

40. Alkaline phosphatase ____ ____ ____
U/L

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

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

H. Vitamin B_{12}

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

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

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

44.

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

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

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

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

____ ____ ____ ____ • ____
pg/mL

I. Prothrombin time, GGT, and HbA1c

Required at visits f048, f096, and f120.

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

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

50.

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

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

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

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

47. International normalized ratio (INR):

____ • ____

48. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

49. HbA1c: ____ ____ • ____
%

J. Oral glucose tolerance test

Required at visits f048, f096, and f120.

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

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

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

51. Date of blood draw for OGTT:

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

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

52. OGTT results at baseline

a. Serum glucose: ____ ____ ____ mg/dL

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

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

53. OGTT results at 2 hours

a. Serum glucose: ____ ____ ____ mg/dL

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

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

Required at f048, f096, and f120.

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

Yes (1) No (2)
59.

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

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

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

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

57. Leptin: ____ ____ • ____ ng/mL

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

____ ____ ____ • ____ mg/dL

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

L. Pregnancy test

Required at all study visits if applicable.

59. Is pregnancy test applicable:

Yes (1) No (2)
62.

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

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

Date must be the same day as date of visit.

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

Positive (1)
Negative (2)

M. Eligibility check

62. Is this the s1 visit:

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

If No (2) → **64.**

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

( ) Yes (1) → Elig (5) ( ) No (2)

N. Administrative information

64. Study Physician PIN: ____ ____ ____

65. Study Physician signature:

_____

66. Clinical Coordinator PIN: ____ ____ ____

67. Clinical Coordinator signature:

_____

68. Date form reviewed:

____ ____–____ ____ ____–____ ____

day mon year

TONIC

LS - Laboratory Results
Tests Done Only During Screening

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: s 1 ____ ____

6. Form & revision: 1 s 1

7. Study: TONIC 3

B. Screening etiologic tests

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

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

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

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

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

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

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

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

C. Autoantibody studies

9. Date of blood draw for autoantibody tests:

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

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

10. Antinuclear antibody (ANA):

Positive (* 1)
Negative (2)

12.

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

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

11. Is ANA titration greater than 1:80

Yes (* 1) No (2)

C

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

12. Antismooth muscle antibody (ASMA):

Positive (* 1)
Negative (2)

13.

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

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

13. Antimitochondrial antibody (AMA):

Positive (* 1)
Negative (2)

15.

Not available (3)

15.

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

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

14. Is AMA titration greater than 1:80

Yes (* 1) No (2)

C

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

D. Ceruloplasmin

15. Date of blood draw for ceruloplasmin:

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

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

16. Ceruloplasmin ____ ____ • ____ ____
mg/dL

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

b. Is ceruloplasmin below the lower limit of normal:

Yes (* 1) No (2)

C

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

E. Alpha-1 antitrypsin

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

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

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

18. Alpha-1 antitrypsin (A1AT)

____ ____ ____
mg/dL

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

b. A1AT deficiency (physician judgment):

Yes (1) No (2)

Elig

F. Iron

19. Date of blood draw for hemochromatosis screening:

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

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

a. Iron: ____ ____ ____ µg/dL

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

c. Ferritin: ____ ____ ____ ____ ng/mL

20. Is hepatic iron index available:

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

22.

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

G. Administrative information

22. Study Physician PIN: ____ ____ ____

23. Study Physician signature:

_____

24. Clinic Coordinator PIN: ____ ____ ____

25. Clinic Coordinator signature:

_____

26. Date form reviewed:

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

TONIC

LU - Laboratory Results - Tests Required at Visit s2

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

When: Visit s2.

Administered by: Study Physician and Clinical Coordinator.

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: l u 1

7. Study: TONIC 3

B. Hepatic panel

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

8. Date of blood draw for hepatic panel:

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

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

10. Bilirubin (conjugated or direct):

____ • ____
mg/dL

11. Aspartate aminotransferase (AST)

____ ____ ____
U/L

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

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

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

____ ____ ____
U/L

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

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

13. Alkaline phosphatase ____ ____ ____
U/L

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

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

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

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

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

Date must be within 3 months of screening.

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

____ ____ ____ ____ • ____
pg/mL

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

17. Leptin: ____ ____ • ____
ng/mL

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

____ ____ ____ • ____
mg/dL

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

D. Prothrombin time, GGT and HbA1c

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

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

Date must be within 3 months of screening.

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

21. International normalized ratio (INR):

____ • ____

22. Gamma glutamyl transferase (GGT):

____ ____ ____
U/L

23. HbA1c: ____ ____ • ____
%

E. Oral glucose tolerance test

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

24. Date of blood draw for OGTT:

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

Date must be within 3 months of screening.

25. OGTT results at baseline

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

____ ____ ____
mg/dL

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

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

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

a. Serum glucose: ____ ____ ____
mg/dL

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

F. Pregnancy test

27. Is pregnancy test applicable:

Yes (1) No (2)

30.

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

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

Date must be the same day as date of visit.

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

Positive (1)
Negative (2)

G. Eligibility check

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

Yes (1) → Elig

No (2)

H. Administrative information

31. Study Physician PIN: ____ ____ ____

32. Study Physician signature:

_____

33. Clinical Coordinator PIN: ____ ____ ____

34. Clinical Coordinator signature:

_____

35. Date form reviewed:

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

Keyed: ( )

TONIC

MA - Modifiable Activity Questionnaire

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

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

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

5. Visit code: ____ ____ ____ ____

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

7. Study: TONIC 3

B. Administrative information

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

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

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

10. Clinical Coordinator
a. PIN: ____ ____ ____

b. Signature: _____

11. Date form reviewed:

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

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

Modifiable Activity Questionnaire

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

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

Circle one

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

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

Circle one

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

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

Circle one

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

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

Circle one

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

What activities did you compete in?

_____

_____

_____

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

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

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

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

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

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

17. Today's date: ________________________________

TONIC

MR - MRI Report

Purpose: To record liver imaging study results.
When: Visits s2 and f096, if needed.
Administered by: Clinical Coordinator.
Instructions: Upper abdominal MRI is optional. Complete for an upper abdominal MRI done in the year prior to starting screening for TONIC or during screening for TONIC (s2 visit) or done during the f096 window (f096 visit). Answer the items based on review of the imaging report; the Study Physician must review and approve the findings recorded on this form. Attach a copy of the original MR report to this form.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: m r 1

7. Study: TONIC 3

B. Upper abdominal MRI

8. Date of upper abdominal MRI:

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

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

a. Fatty infiltration: (1)
b. Cirrhosis: (1)
c. Hepatomegaly: (1)
d. Hepatic mass: (1)
e. Hepatic hemangioma: (1)
f. Hepatic cyst: (1)
g. Intrahepatic biliary dilatation: (1)
h. Extrahepatic biliary dilatation: (1)
i. Splenomegaly: (1)
j. Ascites: (1)
k. Other features of portal hypertension *(specify):* (1)

_____

_____

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

_____

_____

m. None of the above: (1)

C. Administrative information

10. Study Physician PIN: ____ ____ ____

11. Study Physician signature:

_____

12. Clinical Coordinator PIN: ____ ____ ____

13. Clinical Coordinator signature:

_____

14. Date form reviewed:

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

TONIC

PE - Physical Examination

Purpose: Record detailed physical exam findings.

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

Administered by: Study Physician and Clinical Coordinator.

Respondent: Patient.

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

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: p e 1

7. Study: TONIC 3

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. Weight, 1st measurement:

____ ____ ____ • ____

b. Weight, 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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

a. Circumference, 1st measurement:

____ ____ ____ • ____
waist circumference

b. Circumference, 2nd measurement:

____ ____ ____ • ____
waist circumference

c. Units:

Inches (1)
Centimeters (2)

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

a. Circumference, 1st measurement:

___ ___ ___ • ___
hip circumference

b. Circumference, 2nd measurement:

___ ___ ___ • ___
hip circumference

c. Units:

Inches (1)
Centimeters (2)

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

a. Skin fold, 1st measurement:

___ ___ ___ • ___
mm

b. Skin fold, 2nd measurement:

___ ___ ___ • ___
mm

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

___ ___ • ___
arm circumference

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

___ ___ • ___
arm circumference

e. Units for arm circumference:

Inches (1)
Centimeters (2)

13. Temperature *(Oral)*

a. Degrees: ___ ___ ___ • ___

b. Scale:

Fahrenheit (1)
Centigrade (2)

14. Blood pressure

a. Systolic: ___ ___ ___
mmHg

b. Diastolic: ___ ___ ___
mmHg

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

16. Respiratory rate: ___ ___
breaths/minute

C. Examination findings

17. Skin:

Normal (1)
20.
Abnormal (2)

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

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

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

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

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

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

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

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

_____

e. None of the above: (1)

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

Normal (1)
22.
Abnormal (2)

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

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

_____
specify

22. Neck:

Normal (1)
23.
Abnormal (2)

specify abnormality

23. Lymphatic:

Normal (1)
24.
Abnormal (2)

specify abnormality

24. Chest and lungs:

Normal (1)
25.
Abnormal (2)

specify

25. Heart:

Normal (1)
26.
Abnormal (2)

specify abnormality

26. Abdomen:

Normal (1)
28.
Abnormal (2)

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

a. Ascites: (1)

b. Obese: (1)

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

specify

28. Liver and spleen:

Normal (1)
30.
Abnormal (2)

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

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

____ ____ • ____
cm

b. Splenomegaly: (1)

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

specify

30. Extremities:

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

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

a. Contractures: (1)

b. Muscle wasting: (1)

c. Palmar erythema: (1)

d. Pedal edema: (1)

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

specify

32. Genitourinary/pelvis:

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

specify

33. Nervous system:

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

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

a. Mental status abnormal: (1)

b. Asterixis: (1)

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

_____
specify

D. Tanner Staging

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

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

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

44.

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

40.

Male Tanner Staging

37. Genital stage: ____ 1-5

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

39. Pubic hair stage: ____ 1-5

44.

Female Tanner Staging

40. Breast stage: ____ 1-5

41. Pubic hair stage: ____ 1-5

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

44.

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

____ ____
age in years

E. Ability to swallow study medication

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

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

Yes, patient was able to swallow capsule (1)

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

Elig

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

F. Administrative information

45. Study Physician PIN: ___ ___ ___

46. Study Physician signature:

_____

47. Clinical Coordinator PIN: ___ ___ ___

48. Clinical Coordinator signature:

_____

49. Date form reviewed:

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

TONIC

PF - Focused Physical Examination

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

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: ____ ____ ____ ____

6. Form & revision: p f 1

7. Study: TONIC 3

B. Measurements

8. Height *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

9. Weight *(shoes off)*

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Pounds (1)
Kilograms (2)

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

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

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

a. 1st measurement:

____ ____ ____ • ____

b. 2nd measurement:

____ ____ ____ • ____

c. Units:

Inches (1)
Centimeters (2)

12. Temperature *(oral)*

a. Degrees: ____ ____ ____ • ____

b. Scale:

Fahrenheit: (1)
Centigrade: (2)

13. Blood pressure

a. Systolic: ____ ____ ____ mmHg

b. Diastolic: ____ ____ ____ mmHg

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

15. Respiratory rate: ____ ____ breaths/minute

C. Liver signs

16. Liver and spleen:

Normal (1)

18. ____

Abnormal (2)

17. Abnormality *(check all that apply)*

a. Ascites: (1)

b. Asterixis: (1)

c. Contractures: (1)

d. Hepatomegaly: (1)

If Yes, span from right midclavicular line:

____ ____ • ____ ____ cm

e. Jaundice: (1)

f. Muscle wasting: (1)

g. Palmar erythema: (1)

h. Pedal edema: (1)

i. Spider angiomata: (1)

j. Splenomegaly: (1)

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

_____
specify abnormality

D. Administrative information

18. Study Physician ID: ____ ____ ____

19. Study Physician signature:

_____

20. Clinical Coordinator ID: ____ ____ ____

21. Clinical Coordinator signature:

_____

22. Date form reviewed:

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

TONIC

RD – Study Drug Dispensing and Return

Purpose: To record dispensing and return of study drugs.

When: Visits rz, f004, f012, f024, f036, f048, f060, f072, f084, and f096. Use visit code "n" if drugs are dispensed or returned at a time other than a regular study visit or if a second form is needed at a visit to document returned study drugs.

Administered by: Pharmacist or Clinical Coordinator, reviewed by Study Physician.

Instructions: This form documents dispensing of study drug, return of unused study drug, and return of empty study drug bottles. This form is required at visit rz and every scheduled followup visit thereafter except visit f120. It may be used at unscheduled visits as needed (use visit code n).

Study drugs are dispensed in the quantities specified below:

Visit	*No. of TM series bottles*	*No. of TE series bottles*	*Comment*
rz	2	2	12 week supply
f012	2	2	12 week supply
f024	2	2	12 week supply
f036	2	2	12 week supply
f048	2	2	12 week supply
f060	2	2	12 week supply
f072	2	2	12 week supply
f084	2	2	12 week supply

The patient should be queried about return of empty study drug bottles at all study visits; return of unused study drug is required at the visits at which study drug is dispensed. Each time a patient returns a used study drug bottle to the clinical center, the pharmacist or the clinical coordinator should count and record the remaining number of capsules or softgels in study drug bottles. This form allows recording of the return of up to eight bottles (four TM series and four TE series). If more than four bottles of either series are returned at a time, complete a second form (using visit code "n") to record the information for the remaining bottles.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Date of visit:

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

5. Visit code: ____ ____ ____ ____

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

7. Study: TONIC 3

B. Study drug dispensing

8. Is this a second form for returning additional drug bottles at this visit: Yes (1) No (2)

→ **16.**

9. Will study drug be dispensed today: Yes (1) No (2)

→ **11.**

10. Reason for not dispensing study drug *(check all that apply)*

- **a.** Not a scheduled study drug dispensing visit: (1)
- **b.** Study physician-directed treatment interruption/termination: (1)
- **c.** Unwillingness of the participant to take study drugs: (1)
- **d.** Other *(specify)*: (1)

_____
specify

→ **16.**

TM series

Bottle tear-off label

11.

Affix label here

12.

Affix label here

TE series

13.

Affix label here

14.

Affix label here

15. How were the study drugs dispensed to the patient *(check only one)* :

In person	(1)
Mail	(2)
Other *(specify)*	(3)

_____
specify

C. Study drug return

16. Were any TM series bottles returned at this visit:

Yes (1) No (2)

→ **22.**

17. Number of TM series bottles returned *(if more than 4 bottles returned, complete a second RD form)*:

___
(1-4)

	a. Bottle No.	**b. Number of capsules returned**
18.	TM ___ ___ ___ ___	___ ___ ___ (00-100)
19.	TM ___ ___ ___ ___	___ ___ ___ (00-100)
20.	TM ___ ___ ___ ___	___ ___ ___ (00-100)
21.	TM ___ ___ ___ ___	___ ___ ___ (00-100)

22. Were any TE series bottles returned at this visit:

Yes (1) No (2)

28. ◄

23. Number of TE series bottles returned *(if more than 4 bottles returned, complete a second RD form)*:

(1-4)

	a. Bottle No.	**b. Number of softgels returned**
24.	TE ___ ___ ___ ___	___ ___ ___ (00-100)
25.	TE ___ ___ ___ ___	___ ___ ___ (00-100)
26.	TE ___ ___ ___ ___	___ ___ ___ (00-100)
27.	TE ___ ___ ___ ___	___ ___ ___ (00-100)

D. Remaining bottles

28. Are any additional bottles being returned:

Yes (* 1) No (2)

**If yes, complete a second RD form using visit code "n."*

E. Administrative information

29. Clinical Coordinator PIN: _____ _____ _____

30. Clinical Coordinator signature:

_____

31. Date form reviewed:

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

TONIC

RG - Registration

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

When: At first screening visit (s1).

Administered by: Clinical Coordinator.

Respondent: Patient and guardian.

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

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: ____ ____ ____ ____

3. Patient code: ____ ____ ____

4. Visit date:

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

5. Visit code: s 1 ____ ____

6. Form & revision: r g 1

7. Study: TONIC 3

B. Consent

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

Yes (1) No (2)

STOP

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

Yes (1) No (2)

STOP

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

Yes (1)
No (2)

STOP

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

C. Information about patient

11. Date of birth:

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

Record 4-digit year for date of birth.

12. Age at last birthday: ____ ____
years

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

Yes (1) No (2)

Elig

14. Gender:

Male (1)
Female (2)

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

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

17.

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

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

_____
specify

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

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

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

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

_____
specify

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

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

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

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

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

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

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

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

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

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

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

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

D. Source of patient

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

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

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

_____
specify

E. Previous registration in a NASH CRN study

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

(Yes 1) (No 2)

30.

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

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

_____
specify

28. ID Number previously assigned to patient *(record patient ID in item 2):*

___ ___ ___ ___

29. Code previously assigned to patient *(record patient code in item 3):*

___ ___ ___

31.

F. ID assignment

(If a STOP or ineligible condition was checked in section B, the patient is ineligible and a Patient ID should not be assigned. If the patient was previously registered in a NASH CRN study, a new ID number should not be assigned.)

30. Place ID label below and record Patient ID in item 2 and patient code in item 3.

CCCC ####,zzz

G. Administrative information

31. Clinical Coordinator PIN: ___ ___ ___

32. Clinical Coordinator signature:

_____

33. Date form reviewed:

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