NASH CRN

Nonalcoholic Steatohepatitis

Clinical Research Network

Cysteamine Bitartrate Delayed-Release for the Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in Children (CyNCh) Trial

Standard Operating Procedures

Part I: Clinical Center Operations

21 March 2013

CyNCh SOP Part I: Clinical Center Operations

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1.1. Design synopsis

Title	Cysteamine Bitartrate Delayed-Release for the Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in Children (CyNCh) Trial
Sponsor	NIDDK
Type of trial	Phase IIb randomized placebo controlled clinical trial
Objective	To evaluate whether 52 weeks of treatment with delayed release (DR) cysteamine improves NAFLD compared to treatment with placebo
Study design	Multicenter, double-masked, placebo-controlled study with 2 parallel treatment groups
Treatment groups	Group 1: Cysteamine bitartrate delayed-release (DR) capsules (300 mg, 375 mg or 450 mg orally twice a day) Group 2: Placebo

Study duration (per patient)

- Screening within 90 days of liver biopsy and randomization within 120 days of liver biopsy
- 52 week treatment period
- 24 week post treatment follow-up

Study duration (calendar time)

- Recruitment phase: 9 months
- Follow-up phase: 27 months
- Expected rate of recruitment is 16 patients per clinical center; approximately 2 patients per month

Sample size

- 160 patients (80 per group)

Number of clinics

- 10

Inclusion criteria

- Age 8-17 at screening
- Liver biopsy within 90 days of screening visit and no more than 120 days before randomization
- Clinical history consistent with NAFLD

- Definite NAFLD based on a liver Histology
- No evidence of other liver disease by clinical history or histological evaluation
- Histological severity of NAFLD Activity Score (NAS ≥4)
- Sexually active female participants of childbearing potential (i.e., not surgically sterile [defined as tubal ligation, hysterectomy, or bilateral oophorectomy]) must agree to use of two acceptable forms of contraception at screening and continuing through completion of the study, and to complete a pregnancy test at each study visit. Acceptable forms of contraception include hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 3 months prior to screening, and barrier (condom with spermicide, diaphragm with spermicide). Sexual activity will be ascertained at each study visit for post-menarcheal females and if sexually active, subject must verify use of the same 2 acceptable forms of contraception. For pre-pubescent children, a documented attestation from their parent or guardian will be acceptable
- Must be able to swallow DR Cysteamine capsules
- Signed informed consent from parent or guardian
- Signed informed assent from the child

Exclusion criteria: There will be no exclusion criteria based on race, ethnicity, or gender. Patients who satisfy any of the following exclusion criteria will be ineligible for enrollment in the trial:

1. Participants with a current history of the following conditions or any other health issues that make it unsafe for them to participate in the opinion of the Investigators:
    - Inflammatory bowel disease (if currently active) or prior resection of small intestine
    - Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias)
    - Seizure disorder
    - Active coagulopathy
    - Gastrointestinal ulcers/bleeding
    - Renal dysfunction with a creatinine clearance < 90 mL/min/m^2
    - History of active malignant disease requiring chemotherapy within the past 12 months prior to randomization
    - History of significant alcohol intake (AUDIT questionnaire) or inability to quantify alcohol consumption
    - Chronic use (defined as more than 2 consecutive weeks) of medications known to cause hepatic steatosis or steatohepatitis in the past year:
        - systemic glucocorticoids
        - tetracycline
        - anabolic steroids
        - valproic acid
        - salicylates
        - tamoxifen

- The use of other known hepatotoxins within 90 days of liver biopsy or within 120 days of randomization
- Initiation of medications with the intent to treat NAFLD/NASH in the time period following liver biopsy and prior to randomization
- History of total parenteral nutrition (TPN) use in year prior to screening
- History of bariatric surgery or planning to undergo bariatric surgery during study duration
- Clinically significant depression (patients hospitalized for suicidal ideations or suicide attempts within past 12 months)
- Any female nursing, planning a pregnancy, known or suspected to be pregnant, or who has a positive pregnancy screen.

2. Non-compensated liver disease with any one of the following hematologic, biochemical, and serological criteria on entry into protocol:
   - Hemoglobin < 10 g/dL;
   - White blood cell (WBC) < 3,500 cells/mm^3 of blood;
   - Neutrophil count < 1,500 cells/mm^3 of blood;
   - Platelets < 130,000 cells/mm^3 of blood;
   - Direct bilirubin > 1.0 mg/dL
   - Total bilirubin >3 mg/dL
   - Albumin < 3.2 g/dL
   - International normalized ratio (INR) > 1.4
3. Poorly controlled diabetes mellitus (hemoglobin A1c (HbA1c) > 9%)
4. Evidence of other chronic liver disease:
   - Biopsy consistent with histological evidence of autoimmune hepatitis
   - Serum hepatitis B surface antigen (HBsAg) positive.
   - Serum hepatitis C antibody (anti-HCV) positive.
   - Iron/total iron binding capacity (TIBC) ratio (transferrin saturation) > 45% with histological evidence of iron overload
   - Alpha-1-antitrypsin (A1AT) genotype ZZ or SZ
   - Wilson's disease
5. Children who are currently enrolled in a clinical trial or who received an investigational study drug within 180 days of screening or liver biopsy.
6. Subjects who are not able or willing to comply with the protocol or have any other condition that would impede compliance or hinder completion of the study, in the opinion of the investigator.
7. Failure to give informed consent

1.1. Design synopsis

Outcome measures

- **Primary:**

  Centrally scored assessment of histologic improvement in NAFLD between the baseline liver biopsy to end of 52 weeks of treatment, where improvement is defined as: (1) decrease in NAS of 2 or more and (2) no worsening of fibrosis.

- **Secondary:**
  - Reduction in serum aminotransferase and gamma-glutamyl transpeptidase.
  - Reduction in MRI-determined hepatic fat fraction.
  - Changes to markers of oxidation and anti-oxidant status: maldondialdehyde, F2 alpha-isoprostane, total antioxidant capacity, oxidized LDL
  - Changes in fasting insulin and glucose
  - Changes in weight, height, BMI, and waist circumference
  - Changes in the PedsQL score
  - Changes to any symptoms the patient may have experienced
  - Proportion with a change from a histological diagnosis of definite NASH or indeterminate for NASH to not NASH at end of treatment
  - Individual histological characteristics at end of treatment compared to baseline such as steatosis, lobular inflammation, portal chronic inflammation, ballooning, fibrosis score and stage 1a vs 1b fibrosis
  - Change in mean NAS

Randomization:

- Centrally administered randomization stratified by clinical center and baseline body weight (3 groups: ≤65 kg, > 65-80 kg, > 80 kg)

Visit schedule

- Screening visit must occur within 90 days of liver biopsy and randomization within 120 days of liver biopsy.
- Randomization: Final pre-treatment patient interview followed by web-based randomization into one of 2 groups to receive either DR-cysteamine bitartrate or placebo. The randomization design will be stratified by clinical center and baseline body weight into one of three categories (less than or equal to 65 kg, greater than 65 kg up to 80 kg, or greater than 80 kg) with assignments in permuted blocks of random length within each stratum to achieve a target dose of 9 to 12 mg/kg per day up to a maximum total dose of 600-900 mg per day and dispensing of study drug
- Follow up visits (N=6):
  - 4, 12, 24, 36, and 52 treatment weeks after randomization
  - 76 weeks after randomization (24 weeks after treatment ends)

- Both groups will be administered current standard of care nutrition and exercise recommendations, as a series of one page hand-outs given to participants at randomization and each follow-up study visit (one hand-out per visit). These one-page handouts will include serial strategies to limit screen time, reduce saturated fat, simple carbohydrate and fructose intake, and increase physical activity, as well as fruit and vegetable intake.

Liver biopsy schedule

- Standard of care biopsy prior to screening for the trial
- 52 treatment weeks after randomization

MRI schedule

- Prior to treatment initiation
- 52 treatment weeks after randomization (to coincide with liver biopsy when possible)

Statistical Analysis

- The primary analysis is an intention-to-treat analysis in which the proportions of subjects in the active treatment group (Cysteamine DR orally twice daily) with histological improvement in NAFLD (primary outcome, defined above) is compared with the proportion of subjects in the placebo group in whom there is improvement. The comparison is made using a stratified (by clinical site) Mantel-Haenszel chi-square test; a P-value of 0.05 will be considered statistically significant. Subjects who do not undergo an end-of-treatment biopsy will be counted as not improved.

Sample size and assumptions

- Total of **160** participants in 2 groups of equal size (**80** per group)
- Primary comparison: Cysteamine DR vs. placebo
- Primary outcome measure: histological improvement in NAFLD
- Error protection
  - Type I = 0.05
  - Type II = 0.10 (90% power)
- Uncorrected chi-square test using Dupont and Plummer, Power and Sample size software (1998)
- Missing data: 10% will not have 52 week biopsy and will be considered not improved
- Minimum clinically important difference = 33% relative reduction in percent without clinically important improvement in NAFLD in the active treatment group compared to placebo group.
- Allocation ratio of active treatment to placebo groups = 1:1
- Assumed response rates: Expected percent with no clinically important improvement in NAFLD in the placebo group: 75% (based on TONIC data and assumed background use of medications that may influence histology = 33%)

- Expected percent with lack of clinically important improvement in NAFLD in the cysteamine DR group: 50%

Safety Monitoring

- NIDDK-appointed DSMB will monitor the data for safety and efficacy for outcomes such as hepatotoxicity, pregnancy, and any other outcomes or events identified as safety related.

1.2. Data collection schedule

Assessment/Procedure	Screening Visits	RZ	Follow-up visits Weeks from randomization f04	f12	f24	f36	f52	f76
Consent and HIPAA authorization	X	.	.	.	.	.	.	.
Baseline medical history	X	.	.	.	.	.	.	.
Follow-up medical history	.	.	X	X	X	X	X	X
Review for adverse effects	.	.	X	X	X	X	X	X
Review for concomitant medications	X	X	X	X	X	X	X	X
Alcohol questionnaire AUDIT (A) if interim (I)	A	.	I	I	I	I	I	I
Detailed (D) or focused (F) physical exam	D	F	F	F	D	F	D	D
Liver biopsy*	X*	.	.	.	.	.	X	.
MRI for hepatic fat (optional)	X	.	.	.	.	.	X	.
Nutritional assessment	X	.	.	.	.	.	X	.
Pediatric quality of life	X	.	.	.	.	.	X	X
Liver symptoms questionnaire	X	.	.	X	X	X	X	X
Standard of care materials provided	.	X	.	.	.	.	.	.
Eligibility confirmation	.	X	.	.	.	.	.	.
Study drug dispensing	.	X	X	X	X	X	.	.
Review of study drug adherence	.	.	X	X	X	X	X	.
Labs:								
Complete blood count	X	.	X	X	X	X	X	X
Comprehensive metabolic panel with uric acid	X	.	.	.	X	.	X	X
Hepatic panel with GGT, PT, INR	X	.	X	X	X	X	X	X
Fasting lipid profile	X	.	.	.	X	.	X	X
Fasting serum glucose, HbA1c, and insulin	X	.	.	.	X	.	X	X
Etiologic tests	X	.	.	.	.	.	.	.
Pregnancy tests	X	X	X	X	X	X	X	.
Banking:								
Fasting serum and plasma	X	.	.	X	X	X	X	X
DNA	X	.	.	.	.	.	.	.
Liver tissue	X	.	.	.	.	.	X	.
Closeout form	X	.	.	.	.	.	.	X

Complete blood count: Hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count (WBC), white blood cell differential, platelet count

Comprehensive metabolic panel: calcium, sodium, carbon dioxide, chloride, glucose, potassium, total protein, creatinine, blood urea nitrogen (BUN), uric acid

Hepatic panel: Total bilirubin, direct bilirubin, aspartate aminotransferease (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyltransferease (GGT), albumin, prothrombin time (PT), international normalized ratio (INR)

Lipid profile: triglycerides, total cholesterol, LDL and HDL

Etiologic tests: Hepatitis B surface antigen, hepatitis C antibody, alpha-1-antitrypsin level, ceruloplasmin. Autoantibodies: (ANA, AMA ASMA), serum iron, ferritin and total iron binding capacity (TIBC)

*The liver biopsy during screening is for the patient's evaluation of NAFLD

1.3. Blood draw schedule

		Study visit (wk)						
Procedure/amount in mL	**Screening**	**f04**	**f12**	**f24**	**f36**	**f52**	**f76**	**Total**
Fasting glucose, HbA1c and insulin	5	.	.	5	.	5	5	20
Fasting lipid profile	5	.	.	5	.	5	5	20
Complete blood count	5	5	5	5	5	5	5	35
Comprehensive metabolic panel	5	.	.	5	.	5	5	20
Hepatic panel with GGT, INR, PT	5	5	5	5	5	5	5	35
Etiologic tests	20	.	.	.	.	.	.	20
Plasma	10	.	10	10	10	10	10	60
Serum	20	.	20	20	20	20	20	120
DNA	20	.	.	.	.	.	.	20
Total	95	10	40	55	40	55	55	**350**

Complete blood count: Hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count (WBC), white blood cell differential, platelet count

Comprehensive metabolic panel: calcium, carbon dioxide, chloride, glucose, potassium, sodium, total protein, creatinine, blood urea nitrogen (BUN), uric acid

Hepatic panel: Total bilirubin, direct bilirubin, aspartate aminotransferease (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyltransferease (GGT), albumin, prothrombin time (PT), international normalized ratio (INR)

Lipid profile: triglycerides, total cholesterol, LDL and HDL

Etiologic tests: Hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV), alpha-1-antitrypsin level, ceruloplasmin. Autoantibodies: (ANA, AMA, ASMA), serum iron, ferritin, and total iron binding capacity (TIBC)

1.4. Treatment groups and 'starting' dose at randomization

A patient who has signed or had a parent/guardian sign an informed consent statement and who meets eligibility criteria will be randomly assigned to one of two groups for 52 weeks of treatment:

Group 1: Cysteamine Bitartrate Delayed-release (75 mg capsules)
Group 2: Placebo (75 mg capsules)

Dose amounts of study drug or placebo will be assigned to patients by body weight stratum. Additionally, study drug or placebo will be increased gradually from Week 1 to the end of Week 4. If tolerated, the patient will continue with the dose amount dispensed at Week 4 according to his/her baseline body weight and the dose amount will remain fixed thereafter for the entire 52 week treatment period regardless of change in body weight.

Once the Randomization Checks (RZ) form is keyed and the randomization task is run, the randomization plan that was prepared by the Data Coordinating Center (DCC) will generate the study drug bottle numbers to be given to the patient; note that this will not require real time interaction with the DCC staff member. An assignment will be issued only if the database shows that the patient is eligible, the child/young adult/parent/guardian has signed the assent and/or consent statements, and the patient has had all required baseline data keyed to the database.

Dose increases based on body weight of child at baseline

Study drug will be dispensed in 75 mg capsules (either cysteamine bitartrate delayed- release or placebo). Daily dosage will be based on body weight at baseline and increased gradually beginning at Week 1 through the end of Week 4. The dose amounts dispensed at Week 4 will be the prescribed dose for the patient's weight stratum and, if tolerated, will remain fixed at that dose regardless of subsequent weight changes.

For children with baseline weight ≤65 kg:
Week 1: One 75 mg capsule in the morning and 1 in the evening (150 mg/day)
Week 2: Two 75 mg capsules in the morning and 2 in the evening (300 mg/day)
Week 3: Three 75 mg capsules in the morning and 3 in the evening (450 mg/day)
Week 4: Four 75 mg capsules in the morning and 4 in the evening (600 mg/day)

For children with baseline weight >65 kg - 80 kg:
Week 1: Two 75 mg capsules in the morning and 2 in the evening (300 mg/day)
Week 2: Three 75 mg capsules in the morning and 3 in the evening (450 mg/day)
Week 3: Four 75 mg capsules in the morning and 4 in the evening (600 mg/day)
Week 4: Five 75 mg capsules in the morning and 5 in the evening (750 mg/day)

1.4. Treatment groups

For children with baseline weight > 80 kg:
Week 1: Three 75 mg capsules in the morning and 3 in the evening (450 mg/day)
Week 2: Four 75 mg capsules in the morning and 4 in the evening (600 mg/day)
Week 3: Five 75 capsules in the morning and 5 in the evening (750 mg/day)
Week 4: Six 75 mg capsules in the morning and 6 in the evening (900 mg/day)

Distribution of study drug bottles by visit

The study drug assignment algorithm determining both the treatment assignment and the number of study drug bottles to be dispensed is determined by an automated program based on data recorded and keyed from the RZ form at Randomization.

The purpose of the Study Drug Dispensing and Return (RD) form is to capture data regarding dispensing of study drug bottles to patients. Study drug will be dispensed in 150-count bottles containing 75 mg strength capsules as specified below. A surplus of study drug is available depending on when the patient is scheduled within a time window.

For children with a baseline weight of ≤65 kg:
- rz visit: Two bottles (4 week supply + 2.8 weeks)
- f04 visit: Four bottles (8 week supply + 2.7 weeks)
- f12 visit: Six bottles (12 week supply + 4.1 weeks)
- f24 visit: Six bottles (12 week supply + 4.1 weeks)
- f36 visit: Seven bottles (16 week supply + 2.8 weeks)

For children with a baseline weight of >65 kg - ≤80 kg:
- rz visit: Three bottles (4 week supply + 3.6 weeks)
- f04 visit: Five bottles (8 week supply + 2.7 weeks)
- f12 visit: Seven bottles (12 week supply + 3 weeks)
- f24 visit: Seven bottles (12 week supply + 3 weeks)
- f36 visit: Nine bottles (16 week supply + 3.3 weeks)

For children with a baseline weight of > 80 kg:
- rz visit: Three bottles (4 week supply + 2.4 weeks)
- f04 visit: Six bottles (8 week supply + 2.7 weeks)
- f12 visit: Eight bottles (12 week supply + 2.3 weeks)
- f24 visit: Eight bottles (12 week supply + 2.3 weeks)
- f36 visit: Eleven bottles (16 week supply + 3.6 weeks)

If a patient cannot be scheduled for a followup visit before exhausting his supply of study drug, an additional bottle can be dispensed through the Study Drug task.

1.5. Study drug dispensing

At the randomization (rz) visit, two or three of study drug bottles are dispensed based on the child's weight. The data system will print a confirmation of CyNCh randomization and instructions for patient prescription which include the bottle numbers of the study drug to be given to the patient and the CyNCh visit window schedule. Keep the confirmation information for your study files.

At Followup visits, you will need to complete and key the DD (Drug Dispensing Documentation form) prior to followup visits f04, f12, f24, and f36 to receive the patient and visit specific drug bottle numbers. The data system will print a confirmation to CyNCh drug dispensing which includes the bottle numbers of the study drugs to be given to the patient.

If a patient needs additional study drug bottles before the next scheduled visit, you can dispense one bottle by using the visit code 'n' on the DD form and indicate in item 14 that one bottle should be dispensed. The Study Drug Dispensing and Return (RD) form should be keyed for this drug dispensing using a visit code of 'n'.

2. Eligibility and enrollment

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2.1. Inclusion and exclusion criteria

Inclusion criteria

Patients must satisfy all of the following criteria to be eligible for enrollment:

- Children age 8-17 years inclusive.
- Liver biopsy within 90 days of screening visit and not more than 120 days before randomization.
- Clinical history consistent with NAFLD.
- Definite NAFLD based upon liver histology.
- No evidence of any other liver disease by clinical history or histological evaluation
- A histological severity of NAFLD Activity Score (NAS) ≥ 4.
- Sexually active female participants of childbearing potential (i.e., not surgically sterile [defined as tubal ligation, hysterectomy, or bilateral oophorectomy) must agree to utilize the same two acceptable forms of contraception from screening through completion of the study and to complete a pregnancy test at each study visit. The acceptable forms of contraception for this study include hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 1 month prior to screening, and barrier (condom with spermicide, diaphragm with spermicide). Sexual activity will be ascertained at each study visit for post-menarchal females and if sexually active, subject must verify use of the same 2 acceptable forms of contraception.
- Participants must be able to swallow DR cysteamine capsules.
- Written informed consent from parent or legal guardian.
- Written informed assent from the child.

Exclusion criteria

Exclusions will not be based upon gender, race, or ethnicity. Participants with a current history of the following conditions or any other health issues that make it unsafe for them to participate in the opinion of the Investigators:

- Inflammatory bowel disease (if currently active) or prior resection of small intestine
- Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias)
- Seizure disorder
- Active coagulopathy (defined as <13,000 cells/mm^3 of blood)
- Gastrointestinal ulcers/bleeding
- Renal dysfunction with a creatinine clearance < 90 mL/min/m2
- History of active malignant disease requiring chemotherapy within the past 12 months prior to randomization
- History of significant alcohol intake (AUDIT questionnaire) or inability to quantify alcohol consumption
- Chronic use (defined as more than 2 consecutive weeks in the past year) of medications known to cause hepatic steatosis or steatohepatitis including:
    - systemic glucocorticoids
    - tetracycline

  - anabolic steroids
  - valproic acid
  - salicylates
  - tamoxifen,
- The use of other known hepatotoxins within 90 days of liver biopsy or within 120 days of randomization
- Initiation of medications with the intent to treat NAFLD/NASH in the time period following liver biopsy and prior to randomization
- History of total parenteral nutrition (TPN) use in the year prior to screening
- History of bariatric surgery or planning to undergo bariatric surgery during study duration
- Clinically significant depression (patients hospitalized for suicidal ideations or suicide attempts within past 12 months)
- Any female who is nursing, planning a pregnancy, known or suspected to be pregnant, or who has a positive pregnancy screen
- Non-compensated liver disease with any one of the following hematologic, biochemical, and serological criteria on entry into protocol:
  - Hemoglobin < 10 g/dL
  - White blood cell (WBC) < 3,500 cells/mm^3 of blood
  - NeutropFHl count < 1,500 cells/mm^3 of blood
  - Platelets < 130,000 cells/mm^3 of blood
  - Direct bilirubin > 1.0 mg/dL
  - Total bilirubin >3 mg/dL
  - Albumin < 3.2 g/dL
  - International normalized ratio (INR) > 1.4
- Poorly controlled diabetes mellitus (hemoglobin A1c (HbA1c) > 9%)
- Evidence of other chronic liver disease:
  - Biopsy consistent with histological evidence of autoimmune hepatitis
  - Serum hepatitis B surface antigen (HBsAg) positive
  - Serum hepatitis C antibody (anti-HCV) positive
  - Iron/total iron binding capacity (TIBC) ratio (transferrin saturation) > 45% with Histological evidence of iron overload
  - Alpha-1-antitrypsin (A1AT) genotype ZZ or SZ
  - Wilson's disease
- Children who are currently enrolled in a clinical trial or who have received an investigational study drug within 180 days of screening or liver biopsy
- Subjects who are not able or willing to comply with the protocol or have any other condition that would impede compliance or hinder completion of the study; in the opinion of the investigator
- Failure to give informed consent

2.2. Guidelines for repeat determinations of eligibility

While certain inclusion and exclusion criteria are more objective and are unlikely to change, others may change over time. Thus, children who are deemed ineligible at the time of initial screening may be re-screened at a later time as follows:

- An ineligible liver biopsy – the children may be re-screened after 12 months at the discretion of the investigator
- Ineligibility determined on measurements of albumin, INR, direct bilirubin, hemoglobin, WBC, neutrophils, total bilirubin, HbA1c and platelet count – the children may be re-screened at the discretion of the investigator
- Unwilling to participate – the participant may be re-screened after 3 months at the discretion of the investigator
- Unable to swallow study pills – if a child learns how to swallow pills, he could be rescreened

2.3. Randomization and eligibility checking

Randomization steps

- Complete collection of baseline data and key baseline data forms.
- Run electronic check on eligibility (i.e., run the Randomization Task, but opt out of randomization and resolve any ineligibility conditions).
- Run the Randomization Task and confirm that you want to randomize the patient "now." This task will officially randomize the patient in CyNCh and the randomization bottle numbers and materials needed in follow-up will be generated (i.e., visit time window schedule)

Randomization

- The date the clinical center runs the Randomization Task and confirms that the patient is to be randomized "now" and the treatment group is assigned is the date of randomization.
- The "time zero" for reckoning the time windows specified on the patient's CyNCh visit time window guide is the date of randomization.

2.4. Guidelines for transferring from NAFLD Pediatric Database 2 to CyNCh

Patients enrolled in NAFLD Pediatric Database 2 who want to enroll in CyNCh

- Transferring NAFLD Pediatric Database 2 patients into CyNCh necessitates that the screening procedures are conducted within the designated eligibility time window (e.g., liver biopsy obtained within 90 days of screening visit and not more than 120 days prior to randomization in CyNCh).
- NAFLD Pediatric Database 2 patients **without** a liver biopsy or a liver biopsy obtained more than one year prior to CyNCh registration are good candidates for screening in CyNCh.
- Physician discretion is recommended for NAFLD Pediatric Database 2 patients **with** a recent liver biopsy as to whether the patient should register for CyNCh; in this scenario, it may be reasonable to wait until the patient has completed their NAFLD Pediatric Database 2 annual t048 visit.
- Recent liver biopsies obtained in the NAFLD Pediatric Database 2 study and within the CyNCh eligibility window (within 90 days of screening and not more than 120 days prior to randomization) may be used for CyNCh screening to determine eligibility.
- Have the patient sign the CyNCh consent or assent form.
- Complete and key the CyNCh Registration (RG) form but do NOT issue a new patient ID number and code.
- Blood for serum and plasma may be used if collected for NAFLD Pediatric Database 2 within 90 days of biopsy used by CyNCh
- Regarding blood for genetics repository:
    - If not already collected, have patient sign the CyNCh genetic consent, collect a sample, and complete the CyNCh Genetic Consent and Blood Collection Documentation (CG) form
    - If blood for genetics testing was already collected, do not send another sample unless the yield was unsatisfactory.
        - If the yield on the sample drawn when the patient screened for the NAFLD Pediatric Database 2 was satisfactory, leave the NAFLD Pediatric Database 2 CG form in the data system and complete the CyNCh CG answering ‘yes’ to question about prior blood draw for the Pediatric Database 2; the patient does not need to sign the CyNCh genetic consent
        - If the yield on the sample drawn when the patient screened for the Pediatric Database 2 was unsatisfactory, have the patient sign the CyNCh genetic consent form and complete the CyNCh CG form; the Pediatric Database 2 CG form should remain in the data system.
- Lab results reported on the Pediatric Database 2 Laboratory Results - Screening and Followup (LR) and Laboratory Results - Test Done Only During Screening (LS) forms may be used on the CyNCh LR and LS forms if they were obtained within the time windows specified on the forms.

2.4. Guidelines for transferring from NAFLD Pediatric Database 2 to CyNCh

- All interviews and patient questionnaires (AUDIT, baseline history, liver symptoms, quality of life) must be completed anew for CyNCh.
- The physical exam (PE) form must be completed anew for CyNCh.
- If the biopsy used for CyNCh is the same one that was used for the NAFLD Pediatric Database 2, the biopsy for CyNCh must meet study medication requirements (e.g., no use of hepatotoxins 90 days prior to liver biopsy or within 120 days of randomization) not imposed in the NAFLD Pediatric Database 2. The Clinical Coordinator should transcribe the Histology data from the Liver Biopsy Histology Worksheet (HW) onto the CyNCh Liver Biopsy Histology Findings (HF) form. The CyNCh Liver Biopsy Materials Documentation (SD) form must be completed; transcribe information from the Pediatric Database 2 SD form. For items relating to slide sequence numbers, transcribe the slide numbers for the slides that were previously sent for the NAFLD Pediatric Database 2 (i.e., only 10 unstained slides need to be sent from a single biopsy). If liver tissue was obtained, the CyNCh Liver Tissue Banking (LT) form must be completed; transcribe information from the NAFLD Pediatric Database 2 LT form. Where the CyNCh LT form asks for the duplicate LT label to be affixed to the LT form, write in the label information from the NAFLD Pediatric Database 2 form and write in the margin "see NAFLD Pediatric Database 2 LT form". There will be more than one form in the data system pointing to the same numbered slides and liver tissue vials (Pediatric Database 2 SD/LT and CyNCh SD/LT forms), but this is okay since the patient enrolled in the Pediatric Database 2.
- If the patient is eventually randomized in CyNCh, have the patient complete CyNCh follow-up visits and forms; you do not need to complete the MV form for the missed NAFLD Pediatric Database 2 visits, but you do need to complete the NAFLD Pediatric Database 2 Closeout (CO) form to suspend the patient's participation in the NAFLD Pediatric Database 2. The CO form can be completed prior to or after randomization in CyNCh, but our advice is to complete it upon randomization in CyNCh. The patient remains enrolled in NAFLD Pediatric Database 2 while participating in CyNCh, but the patient is not subject to completion of NAFLD Pediatric Database 2 visits.
- Retain all NAFLD Pediatric Database 2 forms completed for the patient in the patient's NASH CRN file.
- Retain the patient's NAFLD Pediatric Database 2 visit windows schedule since it will be needed once CyNCh is completed.

Patients registered in NAFLD Pediatric Database 2 but never enrolled, now wants to register in CyNCh

- The patient should be closed out of the NAFLD Pediatric Database 2 by completing and keying the NAFLD Pediatric Database 2 Enrollment Form (EN) form to document the reason(s) why the patient did not enroll in the Pediatric Database 2. Answer as many of the questions in sections B, C, D, E, and F of the form EN as you can, coding an item as 'm' if you do not know the answer; if the patient is eligible for the NAFLD Pediatric Database 2 but is opting to go directly into CyNCh, answer 'no' to item 22 (no longer consents) and check 'Other reason' in item 23c and write in 'opted to go directly into CyNCh.'
- Have the patient sign the CyNCh consent form.

2.4. Guidelines for transferring from NAFLD Pediatric Database 2 to CyNCh

- Complete and key the CyNCh RG form but do NOT issue a new patient ID number and code.
- Blood for serum and plasma may be used if collected for NAFLD Pediatric Database 2 within 90 days of the biopsy used for CyNCh.
- Blood for genetics repository:
  - If not already collected, have the patient sign the CyNCh genetic consent, and collect a sample, and complete the CyNCh CG form.
  - If blood for genetic testing was already collected, do not send another sample unless the yield was unsatisfactory.
    - If the yield on the sample drawn when the patient screened for the NAFLD Pediatric Database 2 was satisfactory, key the Pediatric Database 2 CG form (if not already keyed) and complete the CyNCh CG form answering 'yes' to the question about prior blood draw for the Pediatric Database 2; the patient does not need to sign the CyNCh genetic consent.
    - If the yield on the sample drawn when the patient screened for the NAFLD Pediatric Database 2 was unsatisfactory, then have the patient sign the CyNCh genetic consent form, draw the replacement sample, and complete the CyNCh CG form. The Pediatric Database 2 CG form can remain in the data system.
- Interviews and questionnaires must be completed on the CyNCh forms:
  - If available, data from the Pediatric Database 2 AUDIT (AD) form may be transcribed to the corresponding CyNCh form, but the patient should be queried regarding any change since the previous interviews; the date in item 4 on the CyNCh AD form should be the date you review the information with the patient.
  - The CyNCh Baseline History (BH) form should be completed anew– it is different from the Pediatric Database 2 BG form, and the CyNCh BH form data will help establish that the biopsy is a medication free biopsy (medication use is not an issue with Pediatric Database 2 biopsies).
- The Physical Exam (PE) form must be completed anew.
- If the same biopsy is used for CyNCh that was used for the Pediatric Database 2, the biopsy for CyNCh must meet study medication requirements (e.g., no use of hepatotoxins 90 days prior to liver biopsy) not imposed in the NAFLD Pediatric Database 2. The Clinical Coordinator should transcribe the Histology data from the Histology Worksheet (HW) onto the CyNCh Liver Biopsy Histology Findings (HF) form. The CyNCh Liver Biopsy Materials Documentation (SD) form needs to be completed; transcribe information from the Pediatric Database 2 SD form. For items relating to slide sequence numbers, transcribe the slide numbers that were previously sent for the Pediatric Database 2 (i.e., only 10 unstained slides need to be sent from a single biopsy). If liver tissue was obtained, the CyNCh Liver Tissue Banking (LT) form must be completed; transcribe information from the Pediatric Database 2 LT form. Where the CyNCh form asks for the duplicate LT label to be pasted onto the LT form, write in the label information from the Pediatric Database 2 LT form and write in the margin 'see Pediatric Database 2 LT form'. The Pediatric Database 2 SD and LT forms can remain in the data system.
- Retain all Pediatric Database 2 forms completed for the patient in the patient's NASH CRN file.

2.4. Guidelines for transferring from NAFLD Pediatric Database 2 to CyNCh

Patient registered in CyNCh, but found to be ineligible, now wants to register in the NAFLD Pediatric Database 2

- The patient should be closed out of CyNCh by completing and keying the CyNCh RZ form to document the reason(s) the patient was found to be ineligible.
- Have the patient sign the NAFLD Pediatric Database 2 consent form.
- Complete and key the Pediatric Database 2 RG form but do NOT issue a new patient ID and code.
- Blood for genetics repository:
  - If blood for genetic testing was not already collected, have the patient sign the Pediatric Database 2 genetic consent, collect a sample, and complete the Pediatric Database 2 CG form.
  - If blood for genetic testing was already collected, do not send another sample unless the yield was unsatisfactory, but the CG form must still be completed.
- Interviews and questionnaires must be completed on the Pediatric Database 2 forms.
- If the same biopsy is used for the Pediatric Database 2 that was used for CyNCh, the Clinical Coordinator should transcribe the Histology data from the Histology Worksheet (HW) form onto the Pediatric Database 2 HF form. If slides were previously sent for CyNCh, the Pediatric Database 2 SD form must be completed referencing the slide numbers for the slides that were sent (i.e., only 10 unstained slides need to be sent from a single biopsy). If liver tissue was obtained, the Pediatric Database 2 LT form must be completed. Where the Pediatric Database 2 LT form asks for the duplicate LT label to be affixed to the LT form, write in the label information from the CyNCh LT form and write in the margin ‘see CyNCh LT form’. The CyNCh SD and LT forms can remain in the data system.
- Retain the CyNCh forms in the patient’s NASH CRN file.

These procedures are complicated. Please contact the DCC if you have questions or if you run into problems when trying to key forms or enroll/randomize a patient.

3. Certification

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3.1. Certification overview

What is certification?

- It is a study-related requirement designed to identify the staff responsible for specific data items, data collection procedures, or decisions about eligibility.
- It is a managerial and quality assurance tool for the study.

Who and what does it apply to?

- It applies to:
  - CyNCh staff
  - Each clinical center
- Certification for CyNCh is required before any patient visits or data collection may occur; patients may not begin any screening examinations, sign any consent statements, or complete any study forms until the clinical site has been certified for the study.
- More than one staff member may be certified for a function and it is recommended that more than one staff member be certified for a function.

Why do we require it?

- Primary purpose is to help assure consistent conduct of the study over time, within and across clinics. The conduct of procedures should be similar across patients and in serial testing of the same patient over the duration of follow-up.
- Study procedures may vary from the usual practice of a participating clinical center, but it is important that methods be carried out in the same manner within and across clinical centers.
- It identifies the staff and sites that carry out study procedures and identifies to staff that they and their site are a part of the CyNCh trial.
- It provides a mechanism for tracking who collected key data items or made key decisions.
- The certification process may help a clinic prepare for study activities by presenting the training, facility, and equipment needs in an organized fashion and requiring acquisition or completion of these items before study specific activities may begin.

3.2. Clinical center certification

General comments

- Each clinical center participating in CyNCh must be certified.
- Completion of the Clinical Center Certification (CC) form will be required.
- IRB approval for the CyNCh protocol and consents will be required.

Purpose of clinical center certification

- Provide information regarding how the clinical center will conduct different aspects of the protocol and who will staff the study.
- Guide a clinical center through the steps of getting ready for CyNCh – provide a checklist of what needs to be in place before patient activities begin.

Requirements for certification of a site

- Complete the Clinical Center Certification (CC) form.
- Certify at least one person for each function that requires certification (a person may be certified for more than one function).
- Obtain IRB approval of the most current CyNCh protocol and consent documents.
- Obtain NIDDK Repository approval of your center's IRB approved consent document
- Receive written notice of approval (email) from the Data Coordinating Center that the site is certified.
- Provide assurances that the study participants' protected health information will be kept confidential.
- Provide assurances that the linkable information will not be transmitted to the DCC.

3.3. Personnel certification

Staff functions requiring certification

- Clinical Coordinator
- Pediatrician
- Pathologist
- Data Entry Technician
- Radiologist
- Imaging personnel (optional)

Requirements

- Everyone:
  - Read the CyNCh protocol
  - Complete the Knowledge Assessment (KA) form; this is a written general knowledge assessment about the CyNCh trial (open book)
  - Complete the Personnel Certification (PC) form; this form identifies the functions applied for and provides an assurance of data confidentiality and integrity
- Additional requirements for Pathologist:
  - Be approved by David Kleiner and Elizabeth Brunt
- Additional requirements for Data Entry Technician:
  - Complete the Data Entry Certification/Decertification Request (DC) form
  - Complete the data system tutorial (personnel previously certified as Data Entry Technician do not need to complete the data system tutorial a second time)
- Additional requirements for Radiologist and Imaging personnel:
  - Be approved by Radiology Reading Center
  - Follow instructions indicated in the CyNCh SOP Part VI: MRI Procedure Manual

Process

- Send required materials to the DCC
- The DCC will send written notice of approval for certification or pending certification
- Each staff member will be issued a Personnel Identification Number (PIN)

Staff PINs

- Each staff member certified for at least one function will be issued a PIN which will consist of 3 digits – the first digit will identify the clinical center and the next two digits will be a sequential number assigned by the Data Coordinating Center
- The PIN is used when completing forms
- The Data Entry Technician uses his/her PIN when signing on to the CyNCh data system
- Staff can be certified for more than one function, but will have only one PIN

4. Human subjects

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4.1. Background

Consent to participate in the CyNCh Trial must be completed before screening for CyNCh may begin. The patient must consent to procedures offered to and performed on him/her for screening, as well as those for the follow-up visits which the patient will face in the future.

The consent process is a dynamic process involving explanations, time to think, questions, clarifications, and advice that a patient may seek from relatives, friends, or anybody else considered relevant. We wish to inform the prospective participant, and the parent, as much as possible and as accurately as possible about what will be offered to him/her, how it will be done, what are the reasonable risks and benefits, what are the alternatives, and what is expected of the patient. We wish to answer patients' questions in a consistent and complete way. A consent form signed by the parent and a patient assent form signed by the child or adolescent will be required.

The CyNCh consent process has four major stages:

- The patient (and parent) is asked to consent to screening and randomization into CyNCh.
- The patient (and parent) is asked to sign the HIPAA authorization to disclose protected health information.
- The patient (and parent) is asked to consent to the collection, storage, and use of blood samples for genetic research, which is optional.
- The patient is asked to consent to an MRI assessment, which is optional.

4.2. Institutional review board process

Three prototype consent statements have been prepared for the CyNCh trial:

- Consent for screening and enrollment in CyNCh
- Consent for the collection, storage, and use of blood samples for current and future genetic research (optional)
- Consent for MRI assessment (optional)

Clinics are expected to use these materials in their submissions to their institutional review boards (IRBs) for approval to participate in CyNCh. Each clinical center must send copies of the consent statements to be used at the clinical center, stamped with their IRB's seal, to the Data Coordinating Center prior to initiating patient activities in CyNCh. Data Coordinating Center staff will review and compare the approved local consents to the prototype consents. Specific local additions to and editing of the prototypes may be required at individual institutions, but deletion of material and major rewording of text may need to be explained and justified. Once a consent form has been approved by an institution's IRB, it cannot be changed without the IRB's approval.

The study protocol and consent forms will be submitted to each clinical center's IRB and to the DCC's IRB. Additionally, each clinical center will submit to their IRB any data collection forms or recruitment materials to be used at their site. A clinical center may not initiate any patient contact about CyNCh until the site has IRB approval for CyNCh and the DCC has certified the site for initiation of CyNCh patient activities. All study personnel will have completed training in the Protection of Human Subjects per NIH guidelines.

HIPAA authorization forms will be prepared by each clinical center according to local clinical center institutional requirements and guidelines.

4.3. Consent administration

CyNCh

Patients referred to a clinical center for screening may have heard about CyNCh, but their level of knowledge and expectations may differ. We wish to standardize the consent administration across clinical centers as much as possible. Administration of the CyNCh consents involves two tasks:

(1) A CyNCh staff member (pediatrician or clinical coordinator) must sit down with the patient and parent and review the contents of the statement; explain the risks, benefits, and responsibilities of participation; review the alternatives to participation; and answer questions.

(2) A CyNCh certified pediatrician or clinical coordinator must sign the consent statement, and in addition to the principal investigator, take overall responsibility for the patient's informed and voluntary consent.

Staff at each clinical center should be designated to carry out these tasks. The rationale for requiring that the consent statement be signed by a study physician is to help assure that the physician signing the consent is one who has a broad role in the study.

Generally, the consent statements should be offered to the patient and their parent to read through at least a day before signature is requested. The consent will then be reviewed with the patient by the staff member designated to obtain consent; the consenter may opt to read the statement to the patient, pausing to explain issues as needed. This activity should take place in a quiet, private, and relaxed setting in the clinical center.

The patient and parent should sign the consent statement in the presence of the CyNCh staff member after all questions have been answered and when the patient has asserted orally that he/she is ready to sign the consent. After the patient and parent have signed and dated the consent, the patient should meet with a CyNCh study physician for the physician to sign the consent statement. Ordinarily, this meeting should take place on the same day that the patient signed the consent statement. The physician should ask the patient to confirm his/her voluntary (assent) consent and query the patient about any questions or concerns the patient may have about participation. Both signatures on the consent form must be in a non-erasable ink pen. If the physician cannot meet with the patient on the same day that the patient signs the consent statement, the physician may sign on another day.

Consent for genetic research

The consent for collection and banking of blood for genetic research should be administered in the same way that the CyNCh consent is administered, except that it should not be signed until the patient has been determined to be eligible for the CyNCh trial. Patients who have already consented to collection and banking of blood for genetic research as part of the NAFLD Pediatric Database 2 do not need to sign this consent again as part of the CyNCh trial.

Consent for MRI research

The consent for participation of Magnetic Resonance Imaging (MRI) assessment should be administered in the same way that the CyNCh consent is administered, except that it should not be signed until the patient has been determined to be eligible for the CyNCh trial.

4.4. Time considerations for obtaining consent

- The **CyNCh Consent and HIPAA authorization** must be obtained at the start of the initial screening visit (CyNCh visit s); documents from the referring physician (if any) or from the NAFLD Pediatric Database 2 study should have been reviewed prior to the visit and the patient should be judged eligible for screening prior to the visit. Signature of this consent is required prior to sending the patient for any CyNCh diagnostic tests. A check for signature of this consent statement occurs on the Registration (RG) form.

- A patient may be given the consent statements to review prior to the initiation of the screening visit to meet patient needs with respect to review time. Whenever a consent is first given to a patient for review, it should be made clear to the patient that the consent should not be signed until requested by a CyNCh staff member. Whatever timing is used by a clinic, the patient should be allowed enough time to reflect about the proposed CyNCh procedures, pose questions, and consult with other individuals that he/she considers relevant to their participation in CyNCh. Patients may request and should be given time to "think it over" at home and come back at a later time.

- The **CyNCh Consent for Collection, Storage, and Use of Blood Samples for Current and Future Genetic Research** must be obtained after eligibility for CyNCh has been established during the screening visit or at the randomization visit. If the patient has already consented to genetic banking as part of the NAFLD Pediatric Database 2, the patient does not need to be presented this option as part of the CyNCh trial and does not need to sign this consent. Signature of this consent is required prior to drawing blood for genetic research; a check for signature of this consent statement occurs on the Genetic Consent and Blood Collection Documentation (CG) form. Signature of this consent statement is not required for CyNCh eligibility (i.e., the patient may choose not to participate in the genetic research component of CyNCh).

- The **Patient Consent for Magnetic Resonance Imaging Research, which is optional in CyNCh,** must be obtained after eligibility for CyNCh has been established during the screening visit and prior to randomization. If the patient verbally agrees to an MRI, the patient will be officially consented for the MRI procedure, per the institutional guidelines. A signed consent prepared by the institution where the CyNCh clinic is located is required prior to undergoing an MRI exam; a check for signature of this consent statement occurs on the MRI Consent and Report Form (MR). Signature of this consent statement is not required for CyNCh eligibility (i.e., the patient may choose not to participate in the MRI research component of CyNCh).

4.5. Consent and Assent handling

- Signed consent statements are important legal documents. These signed statements should be kept in the patient's CyNCh clinical center file together with his/her other CyNCh forms and documents. These forms may or may not be a part of the individual's institutional medical record, but are part of his/her study record in the CyNCh trial. Consent statements will be examined during site visits.

- Consents should be annotated with the patient's study identifiers (ID number and code).

- The CyNCh consent statement is an "all or none" form. The patient either accepts it in its entirety and signs it, or does not. The patient must consent to the evaluation procedures, the follow-up evaluations, and the banking of his/her serum, plasma, and liver tissue specimens. If the patient refuses any part, the patient may not enroll in CyNCh. If the patient was previously enrolled in the NAFLD Pediatric Database 2, the patient must also consent to the CyNCh evaluation, follow-up, and banking procedures to enroll in the CyNCh trial.

- The CyNCh Consent for Genetic Research has been made a separate consent statement so that the patient can opt out of genetic research and still participate in the CyNCh trial. If the patients previously consented to DNA banking as part of the NAFLD Pediatric Database 2 study, the patient will not need to sign a new consent unless the amount of blood was considered to be unsatisfactory.

- The CyNCh Consent for Magnetic Resonance Imaging (MRI) Research has been made a separate consent statement so that the patient can opt out of MRI assessment and still participate in the CyNCh trial.

4.6. Informing participants of changes to consent/assent statement after randomization

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As new data become available during the conduct of CyNCh, the consent statements may need to be changed to reflect the current assessment of risks and benefits to participants in the study.

Procedures for dissemination of revisions of consent statements from the DCC

- Changes deemed necessary will be made to the prototype consent statements.
- Revisions of the prototype consent statements will be distributed to sites via a numbered Policy and Procedure Memorandum (PPM) with instructions to submit the revised consent to their IRB

Procedures for reviewing changes to consent statements with participants

- Clinical center personnel will develop a chronology of IRB approved changes to the consent statements used at their site
- At each follow-up visit, staff will use the chronology of consent changes to review with the participant any changes to the consent since the last visit. This review does not require obtaining the participant's signature on a new consent statement, unless the local IRB requires obtaining a signature.
- Review changes to the consent statements with participants at follow-up visits.
- This review process is not intended to be a reaffirmation of consent. The clinical center, if required by their local IRB, may develop procedures for reaffirmation of consent.

4.7. HIPAA considerations

CyNCh study staff have access to patient health information and to patient identifiers, such as name, address, and telephone number. Study records are to be kept in a secure place. Only people working on CyNCh should have access to these records. However, these records could be reviewed to make sure that the study is being done as it should. People who may see medical records supporting study records are:

- Officials of your institution
- Your institution's research ethics committee
- Monitors from the NASH CRN Data Coordinating Center at the Johns Hopkins University, or other individuals selected by the NASH CRN Steering Committee to monitor the study
- Government officials from the Office of Human Research Protections, the National Institutes of Health, or the Food and Drug Administration

Each clinical center should take steps to protect patient privacy. The assigned patient ID number and code should be used to identify patients on forms and in the data files. Personal information such as name, address, and telephone number should be kept only at the clinical center where a patient completes visits.

People outside the clinical center who will receive CyNCh study data include:

- The NASH CRN Data Coordinating Center at the Johns Hopkins University in Baltimore, Maryland (or its successor) to maintain the central study database.
- The NASH CRN Radiology Reading Center, located at the University of California, San Diego, to receive MRI image transfers for analysis as well as imaging data recorded onto CD/DVD and sent via Federal Express. The data sent to the MRI Center are anonymized – identified only by a NASH CRN number and code
- The NASH CRN Data and Safety Monitoring Board to review the CyNCh data for performance and safety.
- The NIDDK Data Repository located at the Research Triangle International (RTI) in North Carolina
- The NIDDK Genetics Repository at Rutgers, the State University of New Jersey in New Brunswick, New Jersey (or its successor) to receive patients' blood to obtain DNA. The blood samples for a particular patient will be identified by the patient's study ID number and code, not by name.
- The NIDDK Biosample Repository at Fisher Bioservices in Germantown, Maryland (or its successor) to receive patients' plasma, serum, and liver tissue. The samples for a particular patient will be identified by the patient's study ID number and code, not by name.

- The NASH CRN investigators, as well as outside researchers, to analyze and report CyNCh trial data. Patient identity will not be disclosed in any reports or publications resulting from the study. While CyNCh is ongoing, the use of CyNCh data must be approved by the NASH CRN Steering Committee and by the research ethics committee at your institution.

Patient agreement to join the CyNCh trial indicates that the patient also agrees to the use of study data as described above. If a patient does not agree to the described uses of study data, the patient may not participate in CyNCh. The only exceptions are refusal to provide blood for genetic research or refusal of MRI procedure; patients may refuse to provide blood for genetic research or refuse the MRI procedure and still enroll in CyNCh.

5. Study visits

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5.1. Overview of visit schedule

The patient-related activities of the CyNCh trial can be divided into 4 phases:

- **Screening for eligibility for enrollment** (1-2 visits over a maximum of 120 days)
  s: consent, registration, liver symptoms questionnaire, baseline history, review of concomitant drugs, physical exam, AUDIT questionnaire on alcohol use, quality of life, three 24-hour food recall, liver biopsy, fasting liver profile, complete blood count, metabolic panel, hepatic panel and GGT, fasting glucose and/insulin/PT and INR, HbA1c, pregnancy test, etiologic tests, nutritional interview, serum and plasma for banking, and MRI (optional)

- **Randomization to treatment** (1 visit)
  RZ: Consent and re-affirmation, review of concomitant drugs, pregnancy test, height, weight assignment to treatment group and dispense study drug

- **Follow-up treatment phase** (6 visits over 76 weeks)

  f04: Follow-up medical history, focused physical exam, review of concomitant drugs, pregnancy test, blood draw for CBC, hepatic panel, review of adverse events, study drug adherence, study drug dispensing, exercise and nutrition counseling

  f12: Follow-up medical history, review of concomitant drugs, review of adverse events, drug dispensing, study drug adherence, focused physical exam, interim drinking history, blood draw for CBC, hepatic panel and GGT, pregnancy test, serum and plasma for banking, liver symptoms questionnaire, exercise and nutritional counseling

  f24: Follow-up medical history, review of concomitant drugs, review of adverse events, drug dispensing, study drug adherence, detailed physical exam, interim drinking history, fasting lipid profile, complete blood count, metabolic panel, liver symptom questionnaire, hepatic panel and GGT, fasting glucose and insulin, HbA1c, pregnancy test, serum and plasma for banking, nutritional counseling, exercise prescription

  f36: Follow-up medical history, review of concomitant drugs, review of adverse events, drug dispensing, study drug adherence, focused physical exam, hepatic panel and GGT, pregnancy test, blood draw for CBC, serum and plasma for banking. nutritional counseling, exercise prescription, liver symptoms questionnaire

  f52: Follow-up medical history, review of concomitant drugs, review of adverse events, study drug adherence, detailed physical exam, health-related quality of life questionnaire, three 24-hour food recalls, liver symptoms questionnaire,

blood draw for CBC, fasting lipid profile, complete blood count, comprehensive metabolic panel, MRI (optional), blood draw for CBC, hepatic panel and GGT, fasting glucose/insulin/fatty acids, HbA1c, pregnancy test, serum and plasma for banking, liver biopsy

- **Post-treatment 24-week washout**

  f76: Follow-up medical history, review of concomitant drugs, review of adverse events, interim drinking history, detailed physical exam, health-related quality of life questionnaire, liver symptoms questionnaire, detailed physical exam, fasting lipid profile, blood for CBC, comprehensive metabolic panel, hepatic panel and GGT, fasting glucose and insulin, HbA1c, serum and plasma for banking, closeout

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
Screening (s) visit		
	ND	Nutrition Data Documentation
	RG	Registration (document consent, sociodemographics, assign IDs)
	BH	Baseline History
	PE	Physical examination (detailed exam)
	SD	Liver biopsy materials documentation
	HW	Liver biopsy Histology worksheet
	HF	Liver biopsy Histology findings (reading at clinical center)
	LT	Liver tissue banking
	AD	Alcohol Use Disorders Identification Test (AUDIT)
	LR	Laboratory results done during screening and follow-up visits
	LS	Laboratory tests done only during screening
	PQ, PR	Parent Quality of Life
	PW, PY	Child/Teen Quality of Life
	CG	Genetic consent and blood collection documentation
	BP	Blood processing for plasma and serum
	MR	MRI consent and report form
	PL	Patient location (patient contact information)
	LP	Symptoms of Liver disease
Randomization (RZ) visit		
	RZ	Randomization checks
	RD	Study Drug Dispensing and Return
4 week follow-up (f04) visit		
	FH	Follow-up Medical History
	DD	Drug Dispensing Documentation
	LR	Laboratory results during screening and follow-up
	PF	Focused Physical Examination
	RD	Study Drug Dispensing and Return
	AE	Adverse Event Report

Phase/ Visit	Form abbr	Procedure
12 week follow-up (f12) visit		
	FH	Follow-up Medical History
	LR	Laboratory results done during screening and follow-up visits
	PF	Focused physical examination
	DD	Drug Dispensing Documentation
	BP	Blood Processing for Plasma and Serum
	LP	Symptoms of Liver disease
	RD	Study Drug Dispensing and Return
	AE	Adverse Event Report
24 week follow-up (f24) visit		
	FH	Follow-up Medical History
	LR	Laboratory results done during screening and follow-up visits
	DD	Drug Dispensing Documentation
	PE	Physical examination (detailed exam)
	BP	Blood Processing for Plasma and Serum
	LP	Symptoms of Liver disease
	RD	Study Drug Dispensing and Return
	AE	Adverse Event Report
36 week follow-up (f36) visit		
	FH	Follow-up Medical History
	LR	Laboratory results done during screening and follow-up visits
	PF	Focused physical examination
	DD	Drug Dispensing Documentation
	BP	Blood Processing for Plasma and Serum
	LP	Symptoms of Liver disease
	RD	Study Drug Dispensing and return
	AE	Adverse Event Report
52 week follow-up (f52) visit		
	FH	Follow-up Medical History
	LR	Laboratory results done during screening and follow-up visits
	SD	Liver biopsy materials documentation
	RD	Study Drug Dispensing and return
	LT	Liver Tissue banking
	PE	Physical examination (detailed exam)

Phase/ Visit	Form abbr	Procedure
	BP	Blood Processing for Plasma and Serum
	MR	MRI Consent and Report form
	PQ, PR	Parent Quality of Life
	PW, PY	Child/Teen Quality of Life
	ND	Nutrition Data Documentation
	LP	Symptoms of Liver Disease
	AE	Adverse Event Report
76 week follow-up (f76) visit		
	BP	Blood Processing for Plasma and Serum
	FH	Follow-up medical History
	PE	Physical examination (detailed exam)
	LR	Laboratory results done during screening and follow-up visits
	PQ, PR	Parent Quality of Life
	PW, PY	Child/Teen Quality of Life
	LP	Symptoms of Liver disease
	CO	Closeout
	AE	Adverse Event Report

As needed: RC, PL, DR, MV, CG, LT, SD, SR, TN

5.3. Guide for screening visits

Before the patient arrives for the visit

- Abstract data from patient's medical records as needed
- Gather the most recent prior liver biopsy slides as available
- Apply labels to forms as appropriate
- Gather specimen collection and mailing materials (labels, tubes, shippers)
- If advisable, alert phlebotomy lab staff of need to obtain plasma and serum samples
- Confirm eligibility with respect to whatever data have been keyed

Procedures

- Obtain signed consent and signed assent for child or adolescent and parent consent
- Obtain permission to abstract data from patient's medical records
- Obtain patient location information
- Initiate data collection for screening and baseline values
  - Physical exam and anthropometry
  - Interview for baseline history (responses may be modified or expanded upon chart review)
  - Laboratory testing
  - Alcohol use questionnaire
- If patient appears eligible at the close of screening visit
  - Schedule patient for second screening visit
  - Schedule patient for any needed etiologic tests
  - Schedule patient for biopsy, if appropriate
  - Schedule patient for MRI exam, if applicable
- Liver biopsy (pathologist should grade slides from most recent eligible biopsy and obtain 10 unstained slides if possible or arrange for biopsy if needed; if arranging for biopsy, prepare for collection of flash frozen liver tissue)
- MRI exam – optional (radiologist should prepare images and complete forms as indicated in the CyNCh SOP VI: MRI Procedure Manual)
- Complete quality of life questionnaire, and additional testing
- Obtain consent for DNA banking (if available)
- Collect blood for genetic specimen banking (2 tubes) and biosample banking (3 tubes)
- Confirm eligibility (hand/eyeball review of unkeyed data)
- Explain to the patient that you will electronically confirm eligibility after keying the data collected at this visit but that since you believe the patient to be eligible, you would like to schedule the patient for randomization

5.3. Guide for screening visits

Data collection forms

- Forms completed for all patients
  - RG - Registration
  - PE - Physical Examination
  - BH - Baseline History
  - SD - Liver Biopsy Materials Documentation
  - HF - Liver Biopsy Histology Findings
  - HW - Liver Biopsy Histology Worksheet
  - LS - Laboratory Results – Tests Done Only During Screening
  - LR - Laboratory Results - Screening and Follow-up
  - AD - Alcohol Use Disorders Identification Test (AUDIT)
  - -- LP - Symptoms of Liver Disease
  - BP - Blood Processing for Serum and Plasma
  - CG - Genetic Consent Documentation (this form documents both consent and refusal)
  - MR- MRI Consent and Report
  - -- PQ, PR - Parent Quality of Life
  - -- PW, PY - Child/Teen Quality of Life
  - ND - Nutrition Data Documentation

- Additional forms required under specific conditions
  - LT - Liver Tissue Banking (if liver tissue was obtained for banking)
  - RC - Rescreen in CyNCH

- Forms completed for all patients

Forms for clinical center use only

- PL - Patient Location
- Medical records release (use local form)

After the patient leaves the clinical center

- Register patient on clinic data system
- Apply labels to forms as needed
- Set up CyNCh chart for patient and file the materials generated at registration that will be used during visits
- Key completed data forms
- Package biopsy slides for sending to the DCC
- Batch ship flash frozen liver tissue specimen (if available) to NIDDK Biosample Repository by overnight delivery service
- Key data collection forms
- Run Randomization Task and re-check eligibility
- Package whole blood tubes for DNA banking for mailing and ship to Genetics Repository
- Submit MRI data to the RRC
- Process blood to serum and plasma and aliquot for banking; store in local freezer until batch sufficient for mailing accumulates

5.4. Randomization visit

Procedures

- Randomization visit to be conducted as a visit separate from the screening visit
- Patient will be randomized to study drug assignment
- Requests for randomizations will be made by clinical centers using a web based application
- A randomization assignment will be issued only if the database shows that the patient is eligible, has signed the consent statement, and has had all required baseline data keyed to the database
- Patient is given the assigned study drugs with a number unique to the patient, instructed about starting the drugs and monitoring for adverse effects, and begins taking study drugs

Data Collection Forms

- RZ - Randomization Checks
- RD - Study Drug Dispensing and Return
- the RD form should be entered into the data system within 48 hours of dispensing study drug to the patient

Comment

- The date of randomization visit is the date for reckoning all follow-up visits

5.5. Visit windows: randomization and follow-up

Randomization must occur within 120 days of liver biopsy

Visit	Window opens: weeks (days) after randomization	Window closes: weeks (days) after randomization	Ideal date
f04	2 weeks+1 day (15 days)	8 weeks (56 days)	4 weeks (28 days)
f12	8 weeks+1day (57 days)	18 weeks (126 days)	12 weeks (84 days)
f24	18 weeks+1day (127 days)	30 weeks (210 days)	24 weeks (168 days)
f36	30 weeks+1 day (211 days)	42 weeks (308 days)	36 weeks (252 days)
f52	44 weeks+1 day (309 days)	54 weeks (448 days)	52 weeks (364 days)
f76	64 weeks+1 day (449 days)	88 weeks (616 days)	76 weeks (532 days)

5.6. Interim (unscheduled) visits or telephone contacts

- Unscheduled visits or telephone contacts may occur as needed. No time windows or minimum time separations are imposed for such visits or contacts.
- Data are not collected at interim visits (i.e., data forms are not completed) unless reporting a death, a serious adverse event, or liver biopsy, or unless study drugs are needed between visits.
- If a liver biopsy is performed for a CyNCh patient at a time other than the baseline and f52, complete the forms related to liver biopsy (SD, LT forms).

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6.1. Assignment of study identifiers

What

- The NASH CRN uses 2 identifiers for patients
  - ID number (4 digits)
  - ID code (3 alphabetic characters)
- These identifiers help assure confidentiality of patient identity

Materials

- ID number and code labels received from the Data Coordinating Center
- Registration (RG) form

When

- Eligibility evaluation visit (visit s)

By whom

- Clinical Coordinator

Procedures

- Complete the CyNCh Registration (RG) form; if the patient remains eligible at the close of the form, assign the ID number and code by peeling a label of the label sheet and affixing it to the specified item on form RG or note ID assigned previously in NASH CRN
- The patient will be known by these IDs for the duration of the NASH CRN, including participation in any other NASH CRN studies
- Key the Registration (RG) form into CyNCh data system; this must be the first form keyed
- The Registration (RG) form should be keyed for each patient screened for CyNCh, including patients already enrolled in the NAFLD Pediatric Database 2

Comments

- Once an ID number and its associated ID code are assigned, these IDs must be used by the patient for the duration of the NASH CRN and cannot be changed
- Do NOT reassign or reuse IDs assigned to patients found to be ineligible or who refuse enrollment

6.2. Baseline History (BH) Form

Who

- Complete for all CyNCh patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries:
  - History of liver disease
  - Liver biopsy History
  - Menstrual History (female patients) and pregnancy status
  - Medical History (answer items based on information from all sources available to you)
  - Medication use currently and in the past 6 months to 1 year (12 months)
  - Willingness to use birth control methods

When

- Visit s (but given that you need to do chart review, this may take multiple visit days)

How

- Mix of interview data and data obtained by chart review
- Other questions on the BH form can be answered by interview with the patient, or use all sources to get the most accurate information that you can

Definitions of hepatic events queried on Forms BH and FH

- The CyNCh trial will be tracking the occurrence of clinically significant hepatic events. These include variceal bleeding, ascites, edema, hepatic encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome or liver cancer. Any occurrence of these should be documented on the FH form. The following guidelines may be useful in defining these events:

  - **Ascites.** The results of abdominal paracentesis and testing of ascetic fluid is the gold standard for the diagnosis of ascites. However, the appearance of ascites on imaging such as ultrasound or CT scan in the setting of portal hypertension is highly suggestive.
  - **Hepatic encephalopathy.** There should be sufficient documentation of a reversible decrease in neurologic function, in the absence of hypoxia, acidosis, drug toxicity, and other metabolic and toxic insults.

- **Hepatocellular carcinoma.** Cirrhosis may predispose patients to develop hepatocellular carcinoma, the most common primary malignant hepatic neoplasm. Physical findings such as ascites, fever, portal hyptertension, and jaundice are associated with hepatocellular carcinoma. Rise in serum alkaline phosphatase and low alpha-fetoprotein (AFP) level and imaging studies for evaluation of liver lesions (tumor) may lead to a liver biopsy for confirmatory diagnosis.
- **Pedal Edema.** Accumulation of excessive watery fluid in lower extremities will be evaluated by the investigator during physical examination.
- **Variceal bleeding.** The results of diagnostic testing including EGD, radionuclide imaging, or angiography, in the setting of portal hypertension should be confirmed.

6.3. Follow-up Medical History (FH) form

Who

- Complete for CyNCh patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries/reviews
  - Alcohol consumption since the last visit (AUDIT)
  - Medical History diagnoses and procedures since the last visit
  - Medication use since the last visit

When

- Follow-up visits: f04, f12, f24, f36, f52, f76.

How

- Mix of interview data and data obtained by chart review
- Drinking items should be obtained by an interview with the patient
- Other questions on the FH form can be answered by interview with the patient, or use all sources to get the most accurate information that you can

---

6.4. Physical examination (PE and PF forms)

Who

- All CyNCh patients

What

- Anthropometry
  - Height
  - Weight
  - Waist circumference (form PE only)
  - Hip circumference (form PE only)
- Vital signs
  - Temperature
  - Blood pressure
  - Resting radial pulse
  - Respiratory rate
- System review (form PE only)
  - Chest and lungs
  - Heart
  - Abdomen abnormalities
  -- Abnormality of extremities
  - Focused liver signs

When

- Detailed physical (form PE) at visit s, f24, f52 and f76
- Focused physical (form PF) at visits f04, f12, f36
- Fasting is irrelevant for Forms PE & PF

How

- Ideally, use a stadiometer for height measurement.
- Ideally, use the Gulick II tape measure for waist and Hip measurement; this device may be obtained from www.fitnessmart.com (608-735-4718, model 67019, listed at $36); it is manufactured by Country Technology Inc: 608-735-4718.

6.5. Height and weight measurements

Height

- Height may be recorded in inches or centimeters
- Two measurements are recorded
- Ideally, a wall-mounted stadiometer with a horizontal measuring block (or fixed angle) is used; other height measuring devices are acceptable
- Follow the manufacturer's recommendation regarding method and frequency of calibration of the stadiometer
- The patient stands erect on the platform with his/her back parallel to the vertical mounted measure scale (but not touching the wall), looking straight ahead with his/her head in the Frankfort horizontal plane (the horizontal plane defined by the lower margin of the bony orbit (the bony socket containing the eye) and the most forward point in the supratragal notch (the notch just above the anterior cartilaginous projections of the external ear)
- The horizontal measuring block is brought down snugly, but not tightly, on the top of the head
- Record the height to the nearest tenth of the unit of measurement (1 decimal place)
- Ask the patient to step away, raise the measuring block, ask the patient to return, and repeat the measurement

Weight

- Follow the manufacturer's recommendation regarding method and frequency of calibration of the scale
- Weight may be recorded in pounds or kilograms
- Two measurements are recorded
- Ideally, weight is measured in the morning after voiding and before breakfast; this should be possible in the CyNCh since most follow-up visits are to be fasting; if this is not possible, try to measure the patient's weight at the same time of day and under the same conditions as the baseline measurements are obtained
- Patient should be wearing light clothing (e.g, short sleeve shirt or blouse or surgical gown), shorts, socks and without shoes; pockets should be empty
- Patient should stand still in the middle of the scale platform with head erect and eyes looking straight ahead
- Record the weight to the nearest tenth of the unit of measurement (1 decimal place)
- Ask the patient to step away, zero the scale, ask the patient to return, and repeat the measurement
- Patients who have limb amputations or who are wearing casts should have weight measured, but note this on the form on the margin (the notes may be keyed at data entry in the General Comments area of the keying)

6.6. Waist and Hip circumference measurements

Waist

- Waist circumference may be recorded in inches or centimeters
- Two measurements are recorded
- Ideally, a Gulick II Tape Measure will be used; this tape measure is designed to eliminate the guesswork by applying a known amount of tension (4 ounces) to the measuring tape; when used properly, tape tension is always 4 ounces; the self-retracting tape is kept at the desired length until the retract button is pushed
- If an ordinary tape measure (without the special 4 ounce tension indicator device) is used, the measurement will be affected by how tightly the tape is pulled
- Patient should be wearing light clothing (e.g, short sleeve shirt or blouse or surgical gown), shorts, socks and without shoes; pockets should be empty
- Ideally, waist circumference is measured in the morning after voiding and before breakfast; this should be possible in the CyNCh since most follow-up visits are to be fasting; if this is not possible, try to measure the patient's waist at the same time of day and under the same conditions as the baseline measurements are obtained
- Patient should stand with feet together
- Pull an appropriate amount of tape out of the housing
- Ask the patient to bare his/her waist
- Wrap the tape once around the waist: the measure should be taken around the abdomen horizontally at the midpoint between the highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line
- Mark the midpoint on both sides of the patient using a washable marker
- Patient may be asked to assist in passing the tape around the abdomen by holding the end of the tape in position
- When the tape is positioned in the horizontal plane at the correct height, the patient should be asked to keep his/her arms at the sides and breathe naturally; ask the patient to breathe in and out and hold at the end of a normal exhalation
- Align the tape's zero line along side of the tape graduations; pull on the end of the tensioning mechanism until you see just one colored bead
- Record the measurement to the nearest tenth (one decimal place)
- Remove the tape, retract the tape, and repeat the procedure
- If the tape cannot be made horizontal across the waist markings, default to the right hip and note this in the margin of the form

6.6. Waist circumference measurement

Hip

- Hip circumference may be recorded in inches or centimeters
- Two measurements are recorded (ideally the two measurements should be within 4 inches (10.2cm) of each other)
- Ideally, a Gulick II Tape Measure will be used; this tape measure is designed to eliminate the guesswork by applying a known amount of tension (4 ounces) to the measuring tape; when used properly, tape tension is always 4 ounces; the self-retracting tape is kept at the desired length until the retract button is pushed
- If an ordinary tape measure (without the special 4 ounce tension indicator device) is used, the measurement will be affected by how tightly the tape is pulled
- Patient should be wearing light clothing (e.g, short sleeve shirt or blouse or surgical gown), shorts, socks and without shoes; pockets should be empty
- Ideally, hip circumference is measured in the morning after voiding and before breakfast; this should be possible in the CyNCh since most follow-up visits are to be fasting; if this is not possible, try to measure the patient's hip at the same time of day and under the same conditions as the baseline measurements are obtained
- Patient should stand with feet together
- Pull an appropriate amount of tape out of the housing
- Ask the patient to adjust his/her clothing to allow measuring the hips over the patient's underwear
- Wrap the tape once around the hips over the underwear: the measure should be taken at fullest part of the hips (maximum extension of the bullocks)
- Patient may be asked to assist in passing the tape around the hip by holding the end of the tape in position
- When the tape is positioned correctly, the patient should be asked to keep his/her arms at the sides and breathe naturally; ask the patient to breathe in and out and hold at the end of a normal exhalation
- Align the tape's zero line along side of the tape graduations; pull on the end of the tensioning mechanism until you see just one colored bead
- Record the measurement to the nearest tenth (one decimal place)
- Remove the tape and repeat the procedure

6.7. Nutrition Data Documentation (ND)

The Nutrition Data System for Research (NDSR) is the most accurate and comprehensive nutrient and food group serving count calculation software available for research purposes. Developed at the Nutrition Coordinating Center of the University of Minnesota's School of Public Health, NDSR is designed for the collection of 24-hour dietary recalls and the analysis of food records, menus, and recipes. NDSR also features an optional dietary supplement data collection module that may be included with 24-hour dietary recall or record protocols. The NDSR Dietary Supplement Assessment Module (DSAM) utilizes the most currently available NHANES Supplement Database with enhancements from NCC and allows for the collection of 24-hour and/or 30-day intake of all dietary supplements and antacids.

NDSR offers standardized dietary assessment methods, interactive interview modules, immediate nutrient calculations, quality assurance features, many hard copy report options and extensive data output files. Designed by researchers for researchers, NDSR features a dietary intake multiple-pass approach that prompts for complete food descriptions, detailed food preparation methods, additions, and diverse amount descriptions. The optional dietary supplement module provides a tiered interview approach that includes a series of data collection screens that prompt for detailed dietary supplement use.

The CyNCh trial protocol calls for three separate 24 hour food recalls to be obtained during screening and again at the f52 follow-up visit.

The Nutrition Data Documentation (ND) form will document completion of the 24-hour food recall using NDS-R on three different days. Centers will save the output files of the three recalls on a CD or USB drive to forward to the DCC twice a year. A copy of the NDSR Record Properties Report for each 24 hour recall conducted should be attached to the ND form. Six key nutritional values will be recorded on the ND form from each 24-hour food recall interview: Energy (kilocalories), Total fat, Saturated Fatty Acids (SFA), Total carbohydrates, Total sugars, and Total protein.

6.7.1. NDSR data collection and processing procedures

Nutrition Data System for Research (NDSR)

- Patient's dietary intake will be assessed via three 24-hour food recall interviews conducted at two visit points (screening and week 52 follow-up)
- Recall interviews will be conducted by a dietitian or trained research interviewer using the NDSR software and database
- The interviewer will conduct the diet recall using the multiple pass method contained in the NDSR computer program preferably in real-time to ensure the highest data quality. However, if necessary, the recall data may be recorded on an intake sheet and entered into the NDSR program at a later date (preferably not more than 24 hours after the interview)
- At the time of the recall interview, the most current version of NDSR should be used (note: the study may span more than one version)

NDSR Project Set-up

- Assign a project folder, name = **CyNCh**, and abbreviation per local standards.
- Select 'Recall' as the Record Type, and '24hr intake' for the Dietary Supplement Assessment Module (DSAM)

Record set-up

- At start of interview, enter following information into the Header page:
  - Participant ID and code (9999-xyz)
  - Date of intake
  - Date of Birth
  - Gender
  - Life Stage Group
  - Interviewer ID
  - Visit number (key 's' for Screening or f52 for the 52-week follow-up visit
  - Site ID (e.g., BCM, CINC, CU, EU)
- In **Notes** section of the Header page, key the following information for each interview as it applies to each interview:
  - in English OR Translator Used (choose one)
  - in person OR on the phone (choose one)
  - by dietician/nutrition research staff OR coordinator (choose one)
  - with Patient, Mother or female guardian; Father or male guardian; Other, specify (Choose all that apply)
- To see how Header Page should look, refer to section, 6.7.2, **NDSR Intake Properties Report** template page

By whom

- Dietitian or trained research staff interviewer

6.7.1. NDSR data collection and processing procedures

Forms

- ***CyNCh Nutrition Data Documentation (ND)*** form (see section 6.7.1 of CyNCh SOP 1)
- **NDSR Record Properties Reports** (see section 6.7.2 of CyNCh SOP 1)

When

- **Screening visit time window (between Baseline and Rz visit) and f52 time window:**
  - Recall interviews may be conducted in-person or via telephone
  - Three recall interviews will take place during the 's' time window (preferably prior to randomization) and during the f52 time window
  - **Note:** If the third recall interview needs to take place on day of randomization, you may key the ND form with data from the first and second recall interviews obtained during the 's' visit and enter the date of the third recall interview and enter '?' for items 19 a-f on the ND form. Edit the third recall information recorded on the ND form after a final NDSR Records Properties Report is provided by the nutritionist (but the data must be entered prior to randomization can occur)
  - At least one of the three recall interviews for both the screening visit and the f52 visit should obtain food intake information from a weekend day
  - At end of first recall interview during both the 's' and f52 visits, request days/times participant and/or parents are available for telephone interviews and obtain best telephone contact information, including a secondary telephone number if available

Recall interview recommendations

- Recommend that the first recall interview during 's' visit (and prior to randomization) be in-person to enable patient and family to meet dietitian, if possible; the standard script (see section 6.7.4) and Food Portion Size Guide (section 6.7.3) should be used
- Recommend that the third recall interview during 's' time window be conducted via telephone if possible to enable timely completion of ND form prior to randomization
- Recommend that the third recall interview during f52 time window may be conducted via telephone to enable timely completion of ND form

Conducting a standardized recall interview

- Recall interview may be conducted with the patient alone (patient $\geq$14 years)
- Recall interview may be conducted with parent/guardian alone (patient $\leq$10 years)
- Recall interview may be conducted with patient and parent/guardian together at any age

Interview materials

- A visual 'Portion Size Guide' should be used to assist patient and/or parents with estimating amounts of food or beverages consumed. Refer to section 6.7.3, **Food Portion Size Guide**

- Give patient a copy of the **Food Portion Size Guide** to take home and to use for telephone interviews
- If possible, complete the remaining two recall interviews within two weeks of study visit date
- Clinical centers will save all of the output files of the three recall interviews onto a CD or USB drive to forward to the DCC two times a year

Reporting

- ***NDSR Record Properties Report*** to be generated from food recall information obtained during screening and at f52 follow-up visits.
- Data will be keyed into the NDSR during real-time in-person or telephone recall interviews
- Generate and print the ***NDSR Record Properties Report*** for each of the three interviews at both the screening visit and the f52 visit
- Upon completing all three recall interviews with a patient, generate the NDSR Intake Properties Report for each recall and send to the Study Coordinator in pdf format (see section 6.7.2).
- The Coordinator will record relevant data from each of the ***NDSR Record Properties Reports*** onto the ***CyNCh Nutrition Data Documentation (ND)*** form and attach each of the three ***NDSR Record Properties Reports*** to the ***ND form***.
- Note the dates recorded on the ND form in items 8, 12 and 16 should be the date that the interview was done, NOT the "intake" date (date meals were eaten).

Off-Site Dietary Recalls (using CINC CR services)

- When the recalls are being conducted by an off-site center, all three recalls will be completed via telephone. The following procedures apply. At the screening visit, the study coordinator will:
    - inform the family that someone will be calling them at home to conduct the diet recall interviews;
    - Use the standardized script to instruct the family on how to respond to the diet interview and use the **Portion Size Guide** to estimate amounts (if applicable); and
    - Finally, the study coordinator will collect contact information and available days and times in the following two weeks when they will be available to respond to the diet recall interview over the telephone.

NDSR 2012 Record Properties Report

Header Information

Participant ID: #9#9
Participant Name: xyz
Date of Intake: 09/23/2012
Day of Intake: Sunday
Date of Birth: 12/21/2002
Gender: Female
Life Stage Group: Females, age 9-13 y
Interviewer ID: SS
Visit Number: S
Site ID: BCM
Header Notes: Recall administered by dietitian; in English; with mother and patient together; by phone.

Trailer Information

Amount of Intake Was: Close to the amount usually eaten.
Information Was: Reliable
Trailer Notes:

Collection Information

Date of Entry: 09/27/2012
Data Collected in NCC Database Version: 2012
Data Collected in Software Version: 2012
Data Collected in DSAM Database Version: 2012

Project Information

Project Name: Summer Quarter 2012 CyNCh Study SSS
Project Abbreviation: SQ12CYSS
Record Type: Recall
DSAM: 24-hour intake
Project Notes:

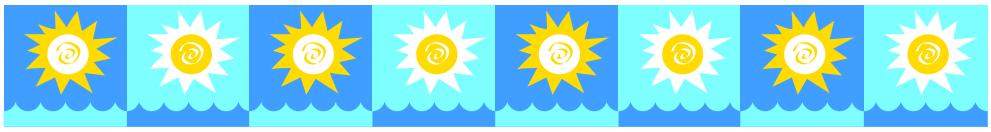
NDSR 2012 Record Properties Report

Selected Nutrients

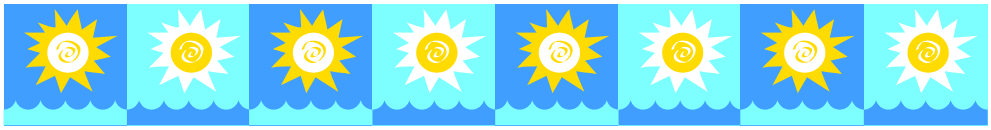
Nutrient	Amount Reported	Daily Value [1]	% Daily Value
Energy (kilocalories)	1285 kcal		
Calories from Fat	390 kcal		
Total Fat	43.889 g	65 g	68 %
Total Saturated Fatty Acids (SFA)	13.633 g	20 g	68 %
Total Trans-Fatty Acids (TRANS)	1.182 g		
Cholesterol	404 mg	300 mg	135 %
Sodium	3537 mg	2400 mg	147 %
Total Carbohydrate	157.916 g	300 g	53 %
Total Dietary Fiber	5.709 g	25 g	23 %
Total Sugars	54.247 g		
Total Protein	63.241 g	50 g	126 %
Total Vitamin A Activity (International Units)	1448 IU	5000 IU	29 %
Vitamin C (ascorbic acid)	9.363 mg	60 mg	16 %
Calcium	365 mg	1000 mg	36 %
Iron	9.004 mg	18 mg	50 %

[1] Daily Values are based on a caloric intake of 2000 kcal per day. Nutrient comparisons are not performed for all nutrients for which a Dietary Value has been established. From: *Code of Federal Regulations, Food and Drugs,* Title 21, Part 101.9, Nutrition labeling of food, 2007.

Note: DSAM nutrients are not included in these totals. Nutrient totals may not equal the sum of their parts. (Refer to the NDSR User Manual.)

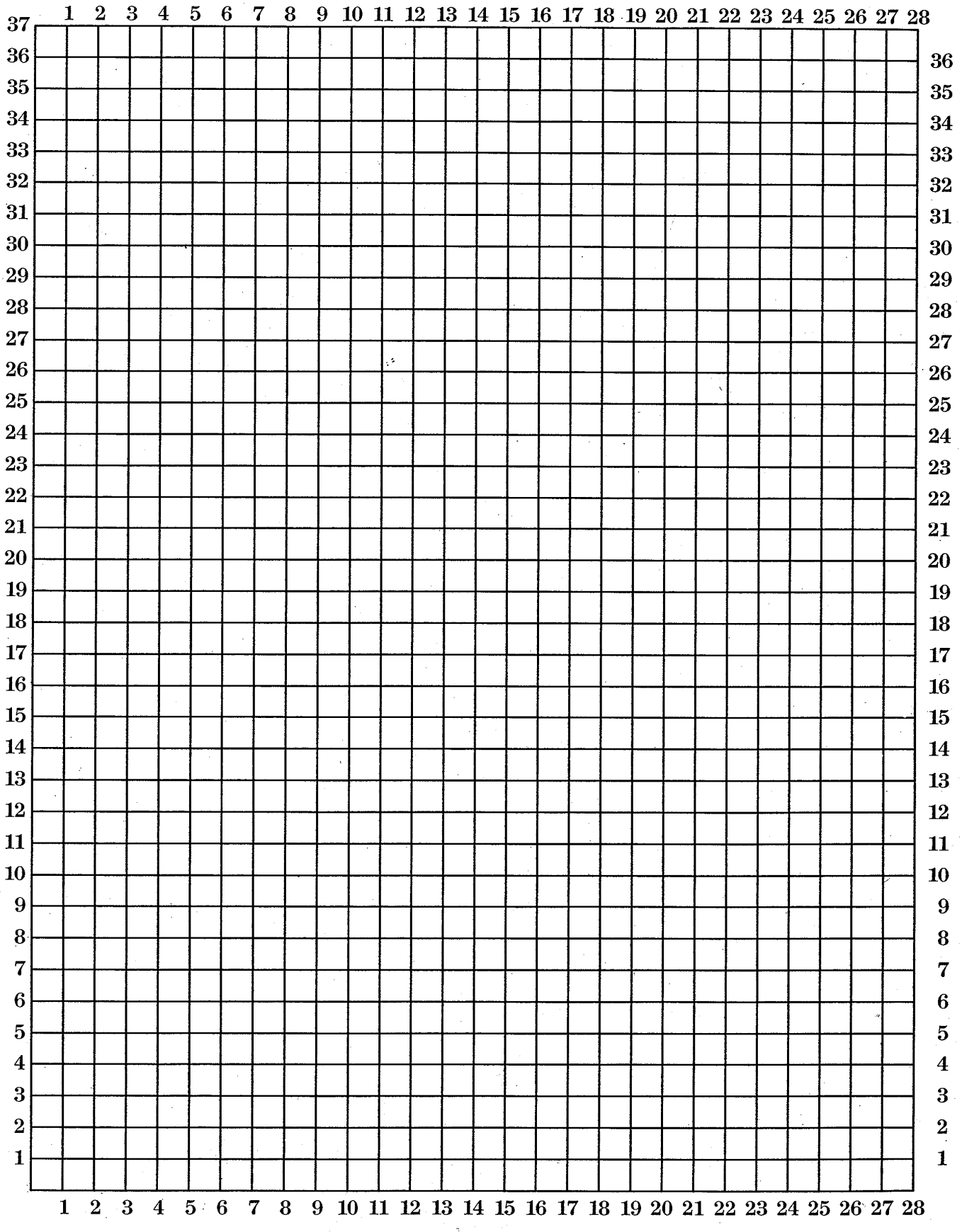


Food Portion Size Guide

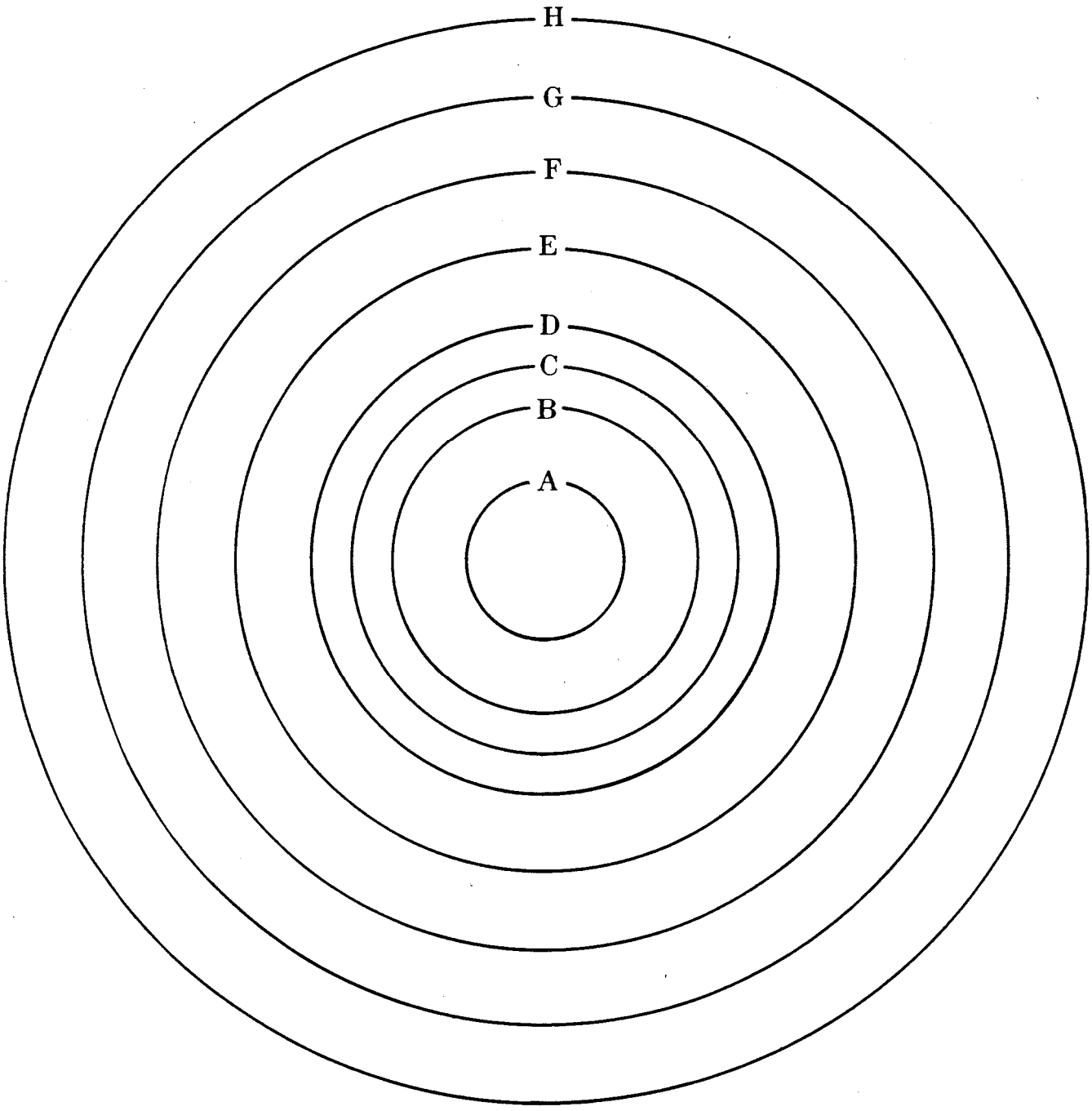


Please keep this packet near your phone

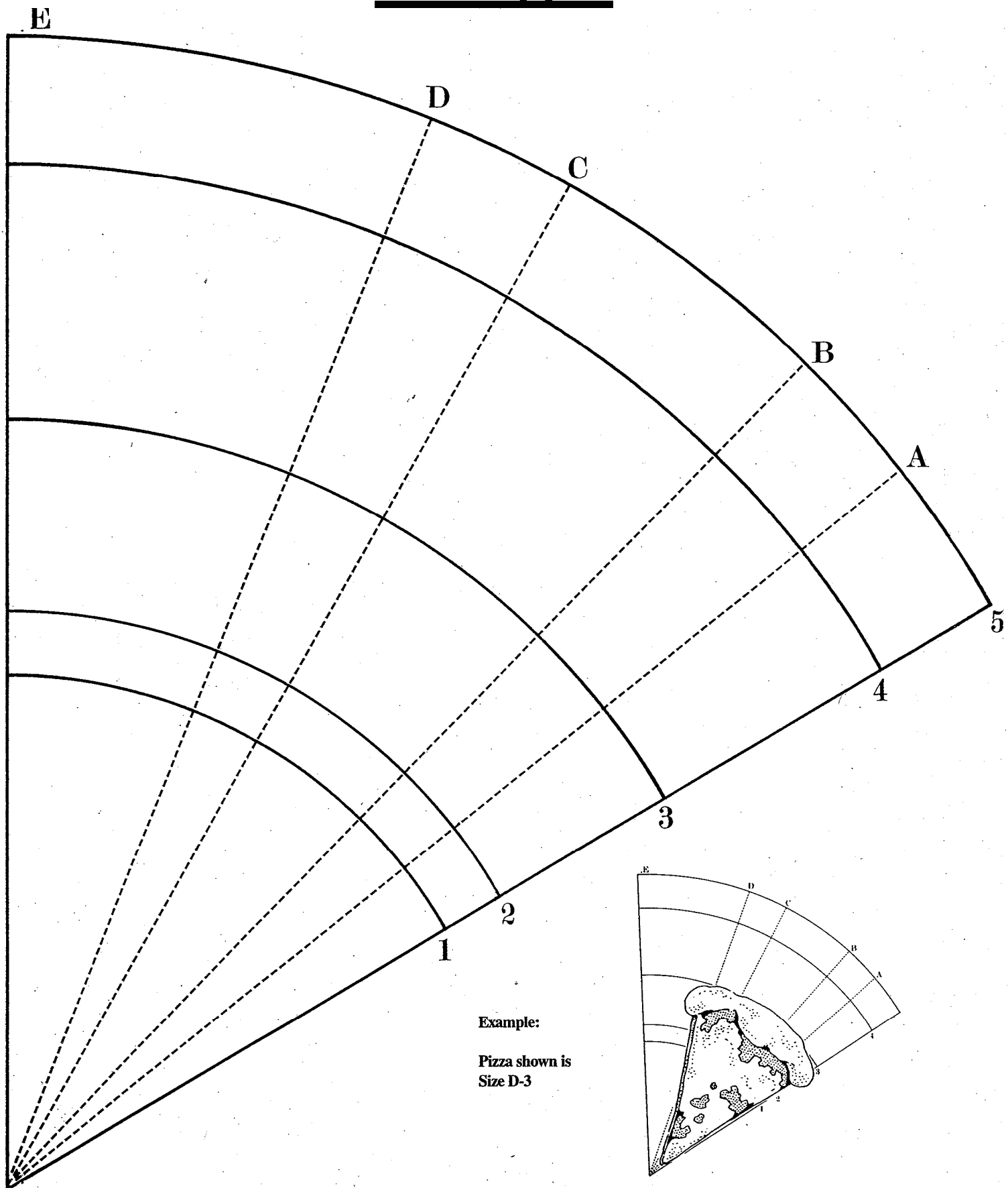
Squares and Rectangles



Circles



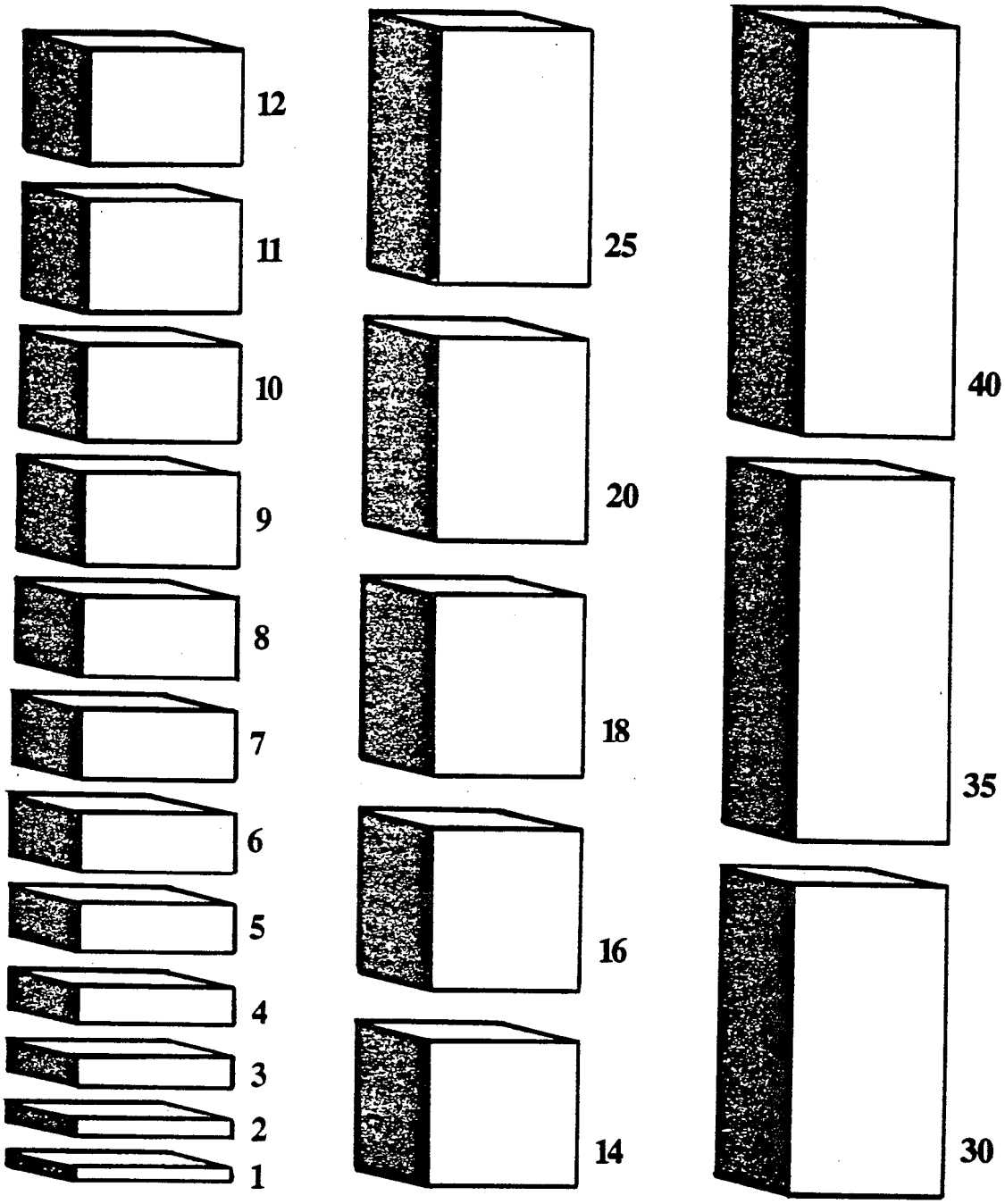
Wedges



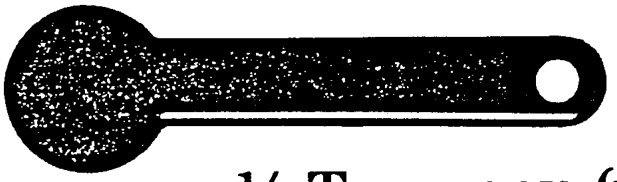
Example:

Pizza shown is Size D-3

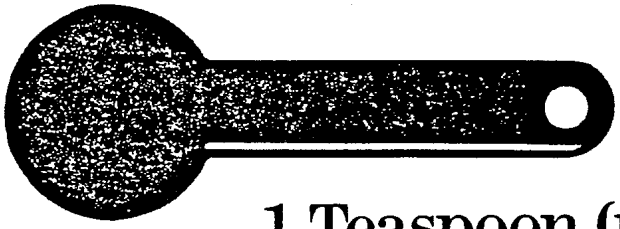
Thickness



Measuring Spoons



½ Teaspoon (tsp)

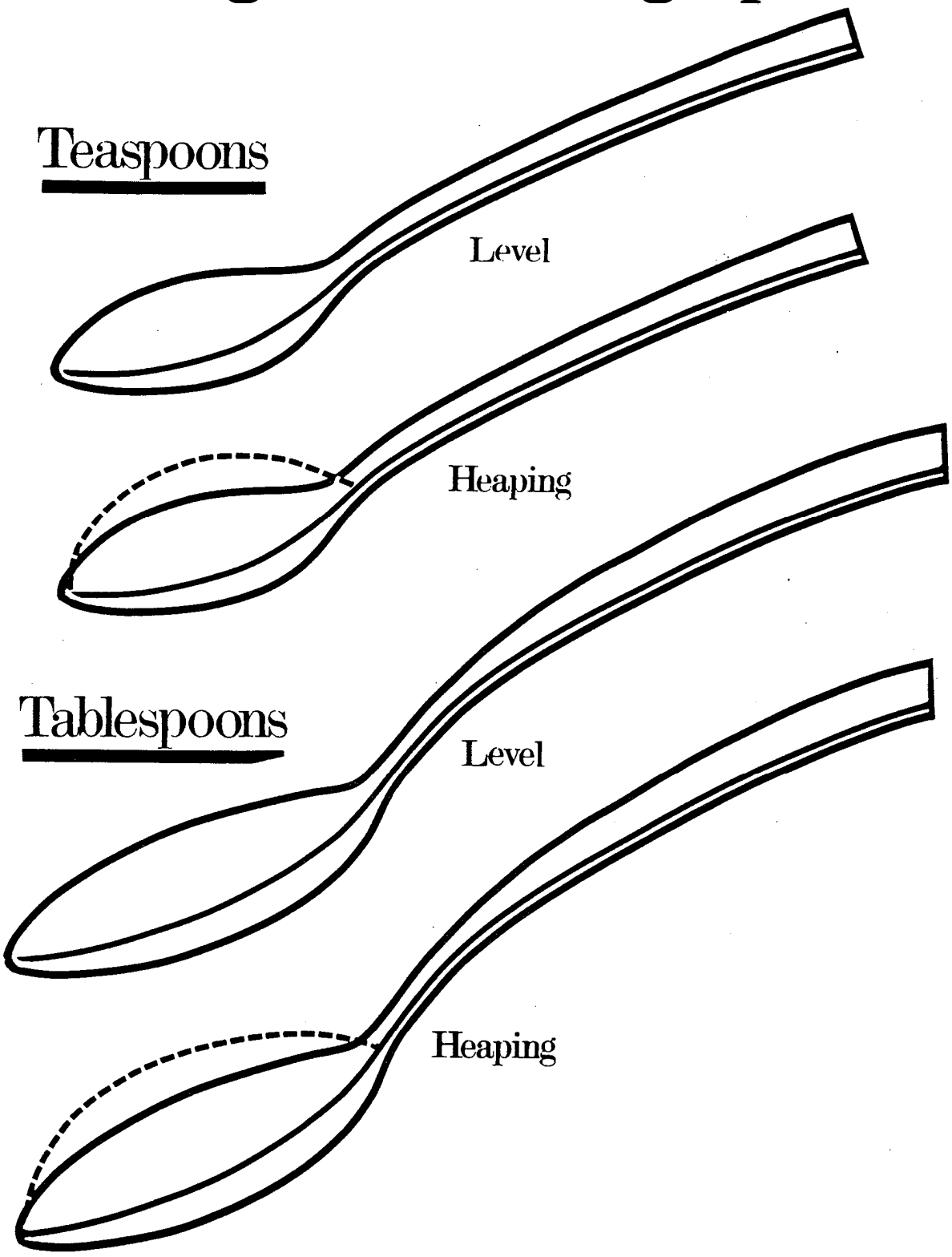


1 Teaspoon (tsp)

½ Tablespoon (Tbsp)

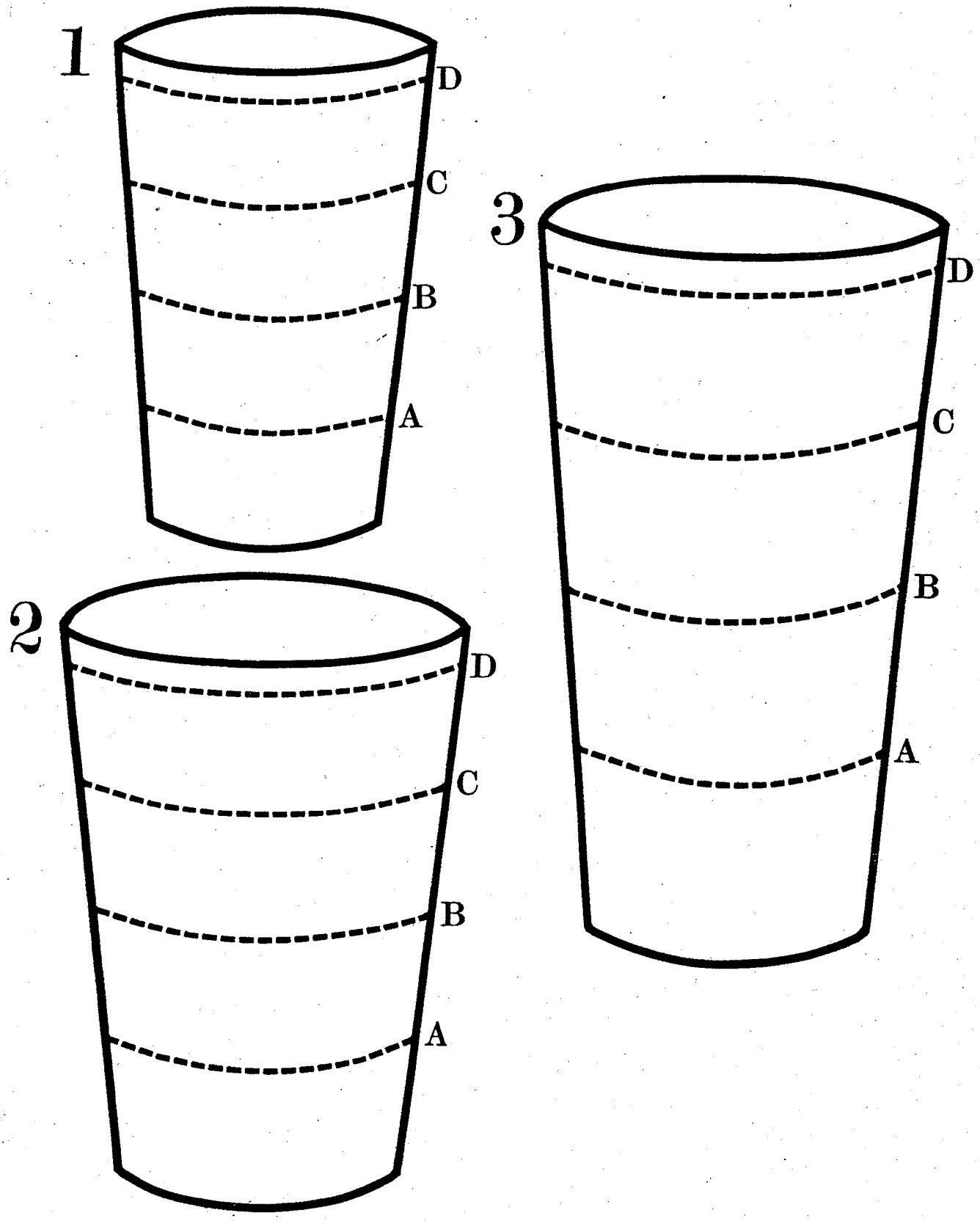
1 Tablespoon (Tbsp)

Eating and Serving Spoons

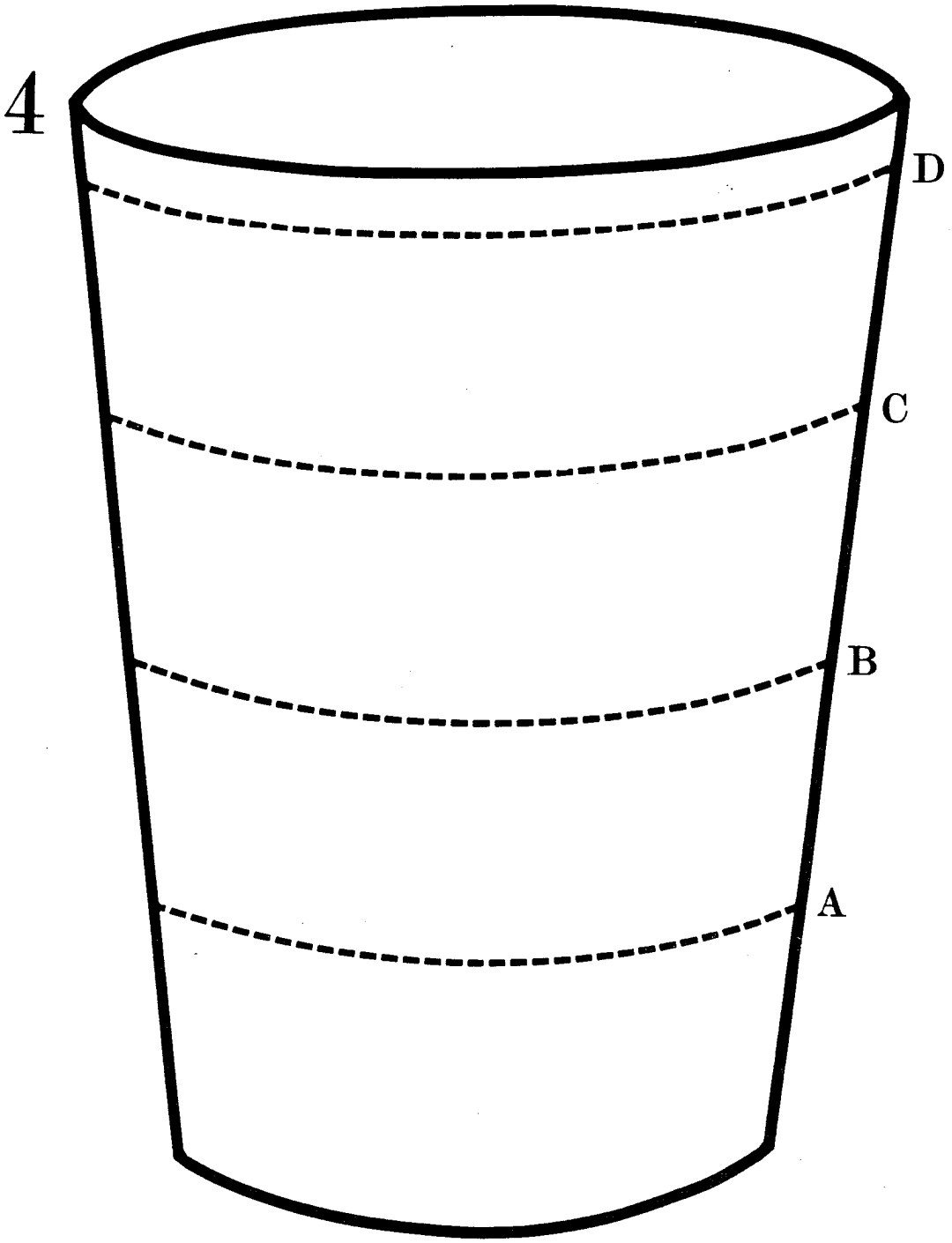


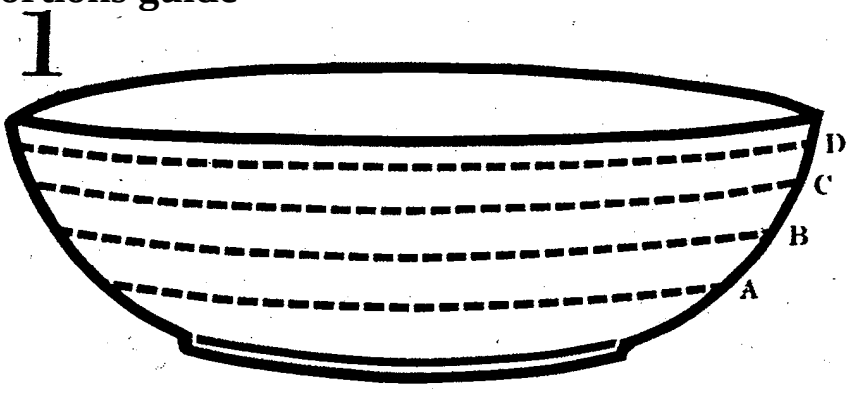
Measuring Cups

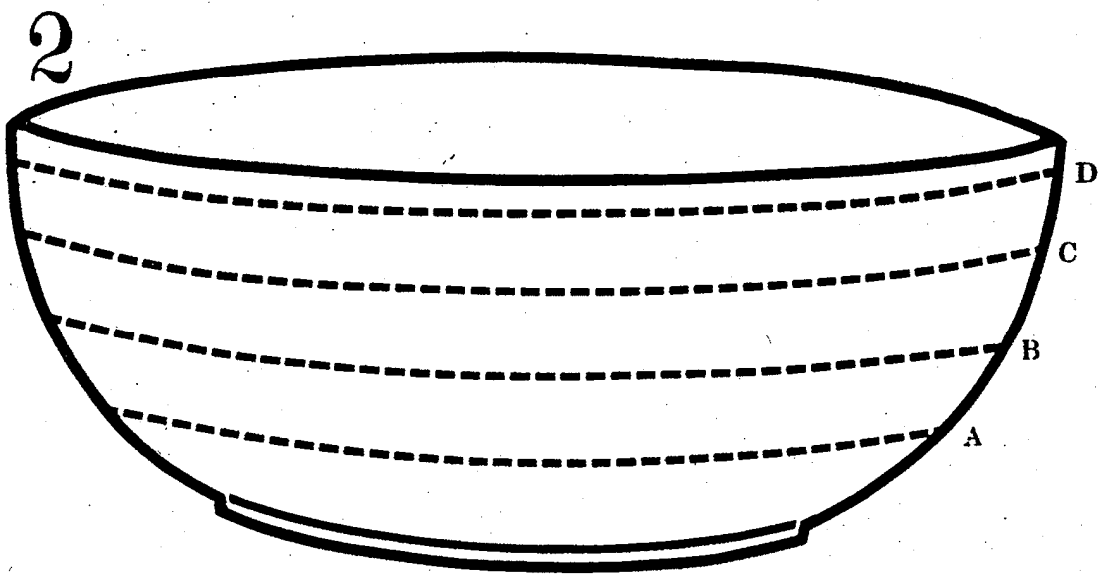
Glasses

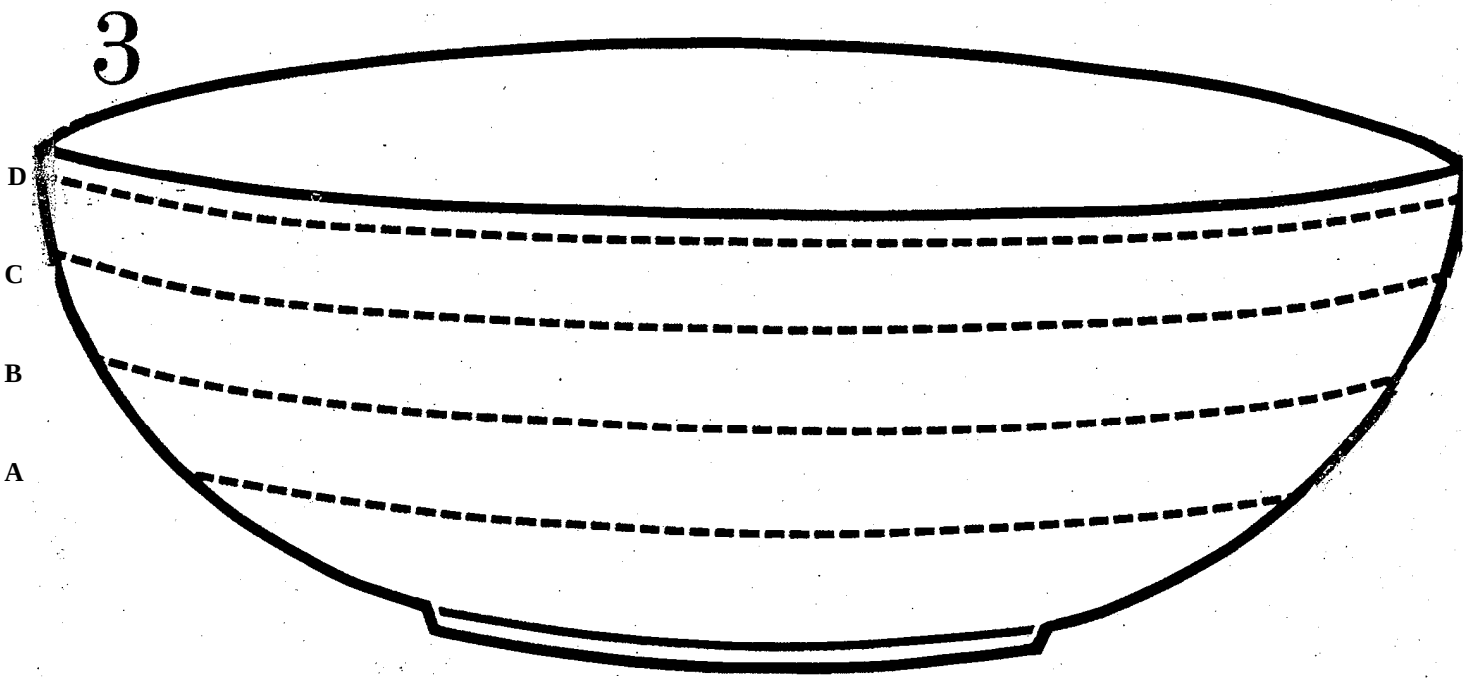


Glasses



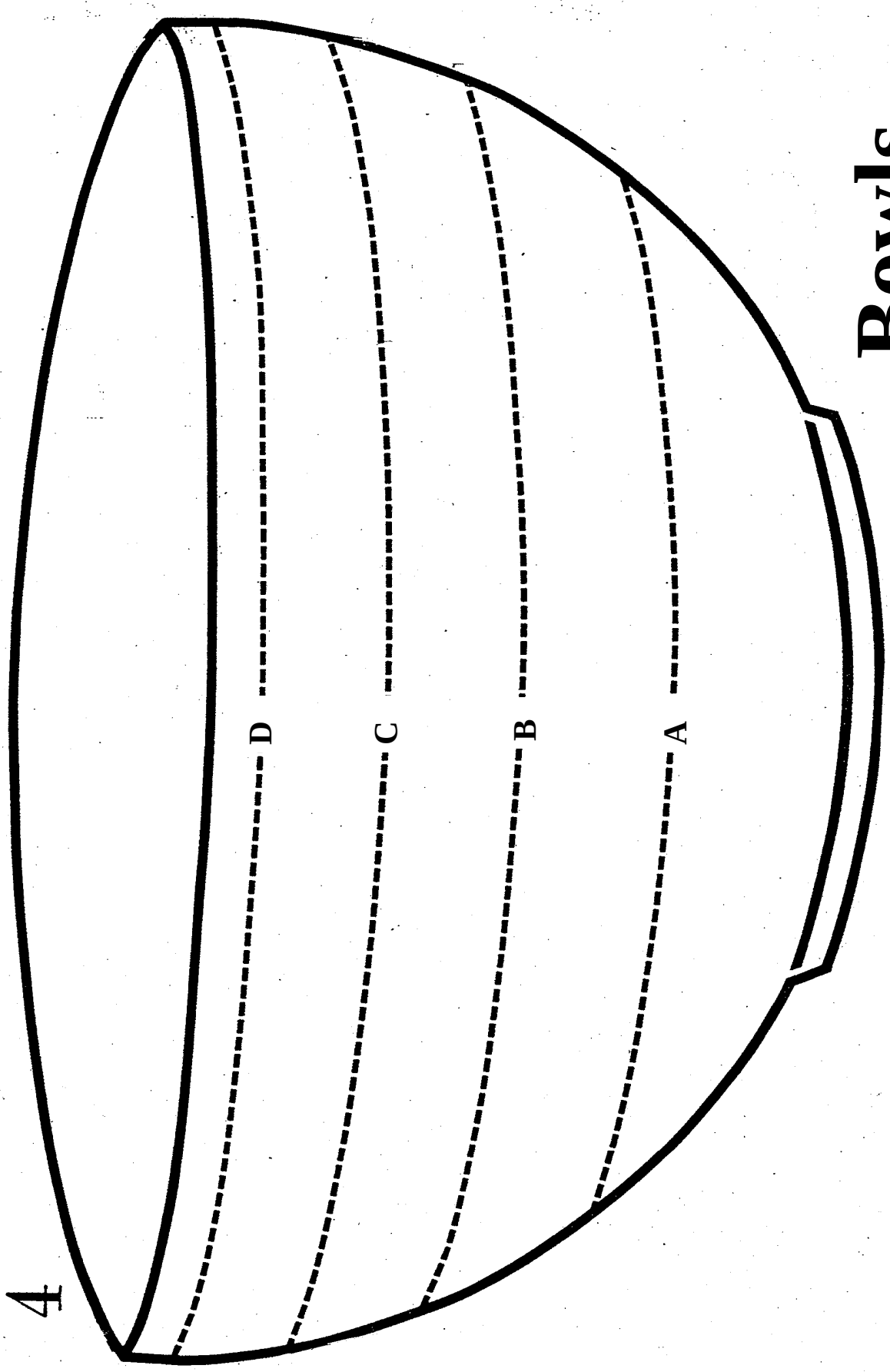






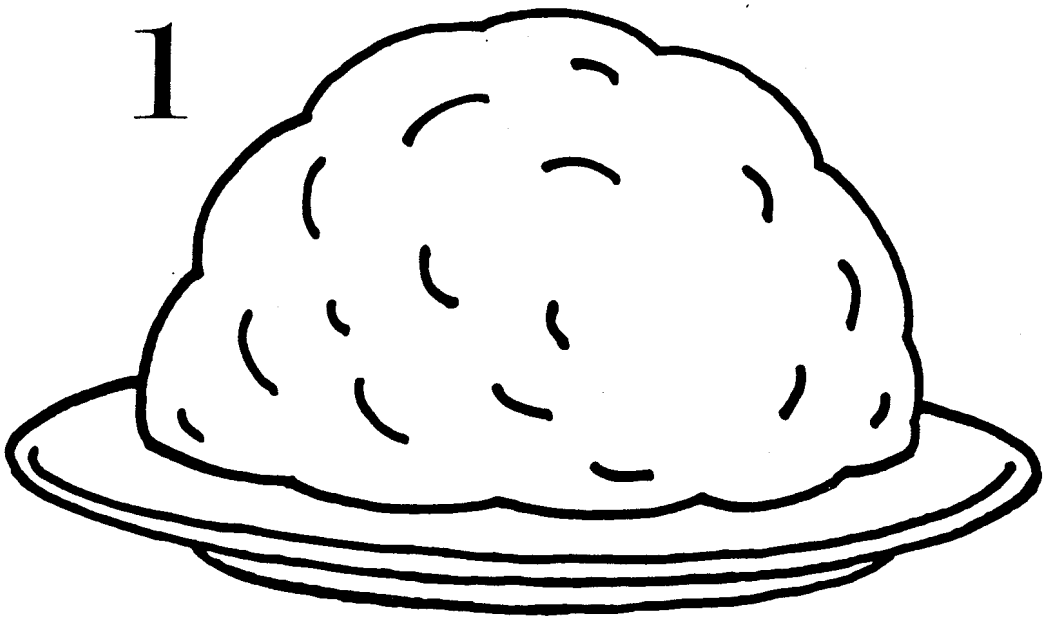
Bowls

Bowls

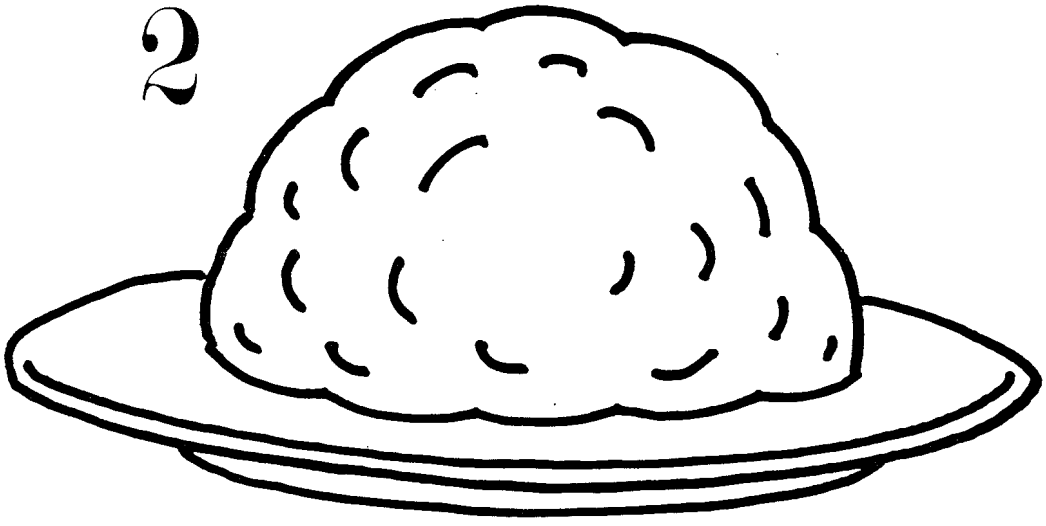


Mounds

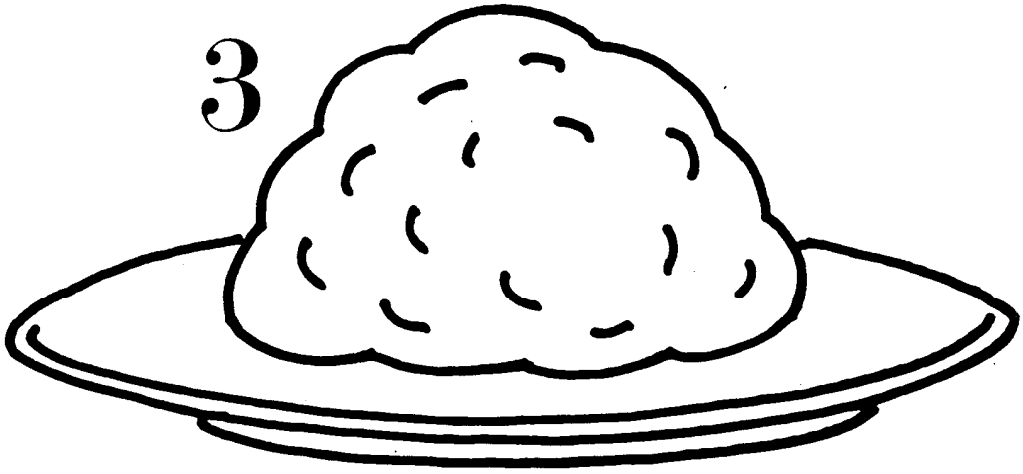
1

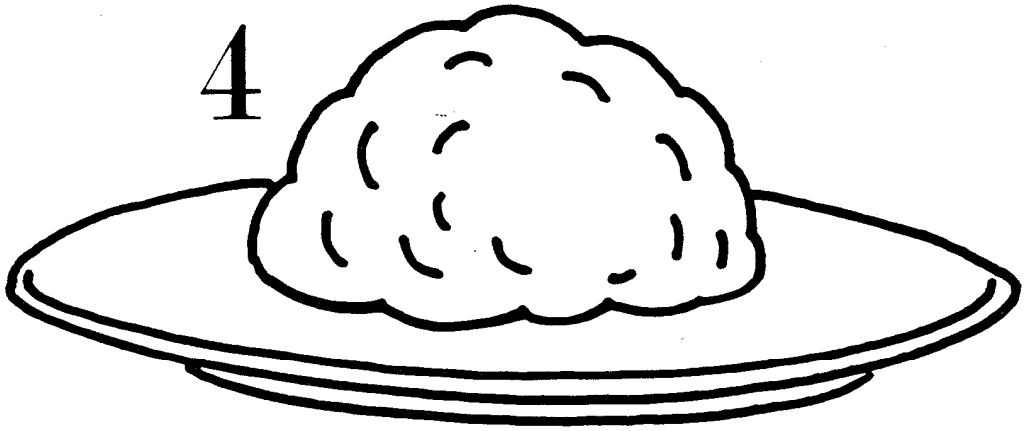


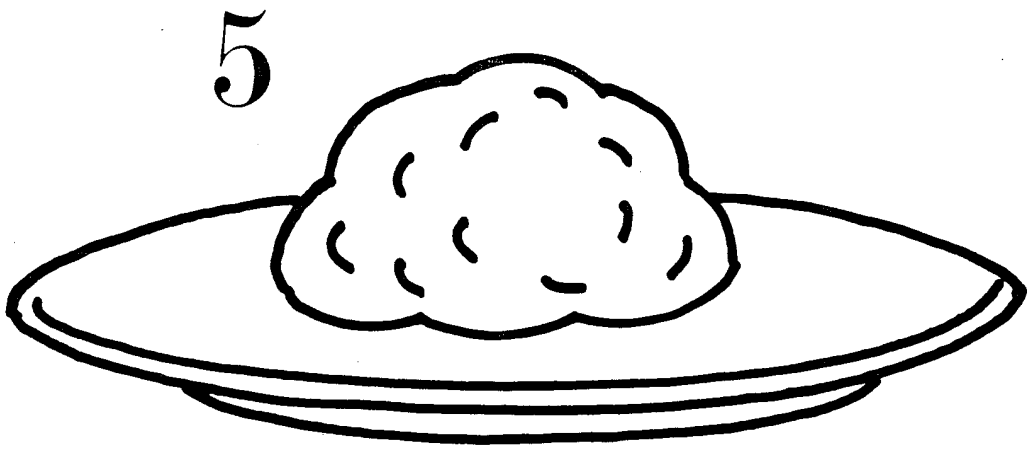
2



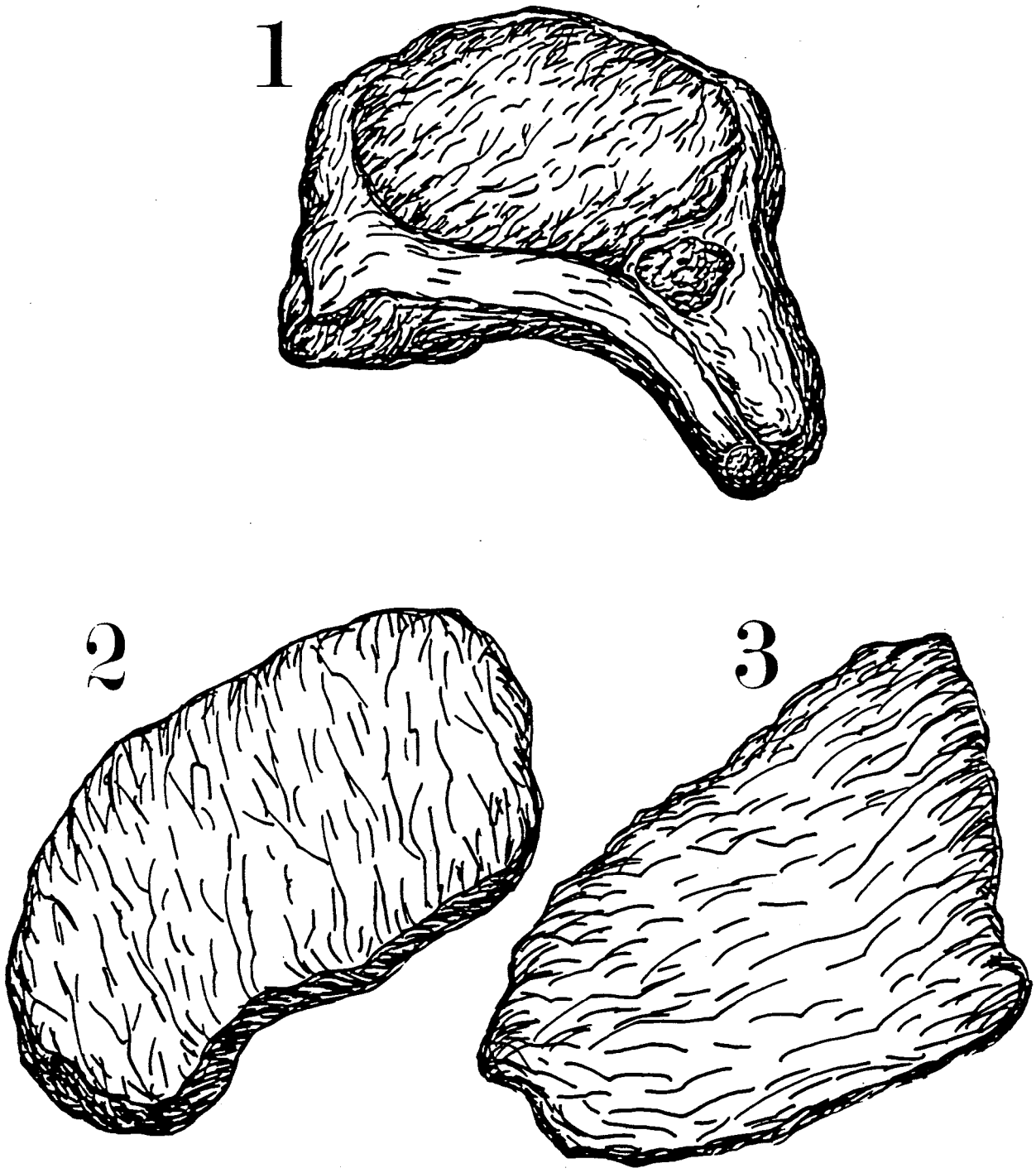
Mounds



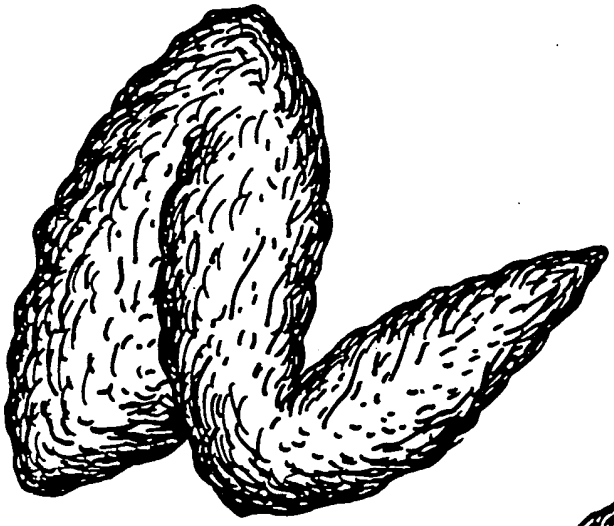




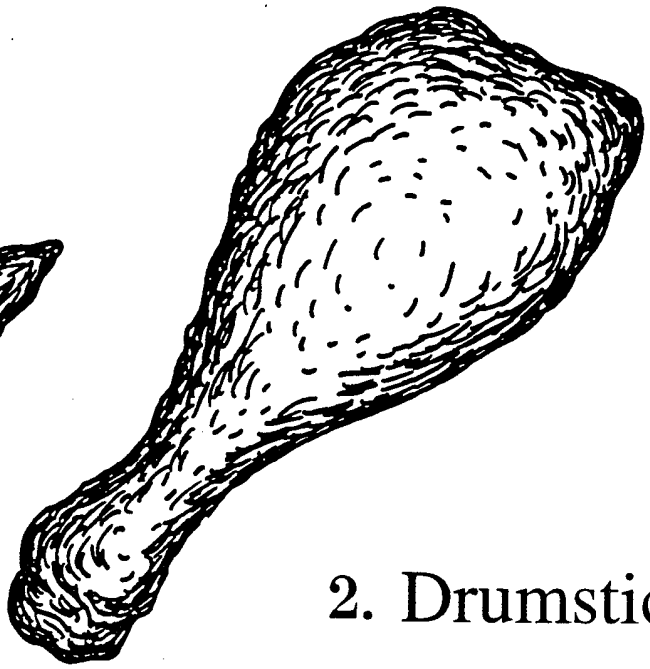
Meats



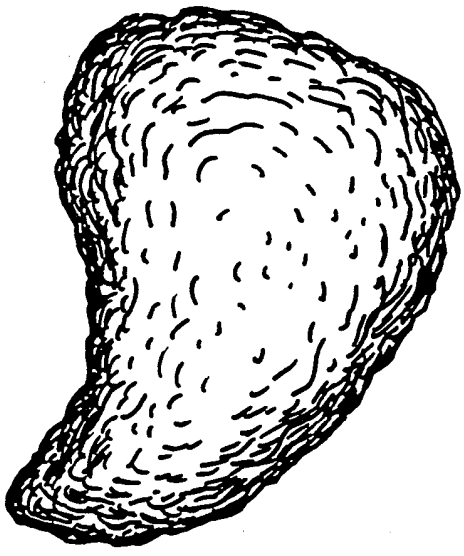
Chicken



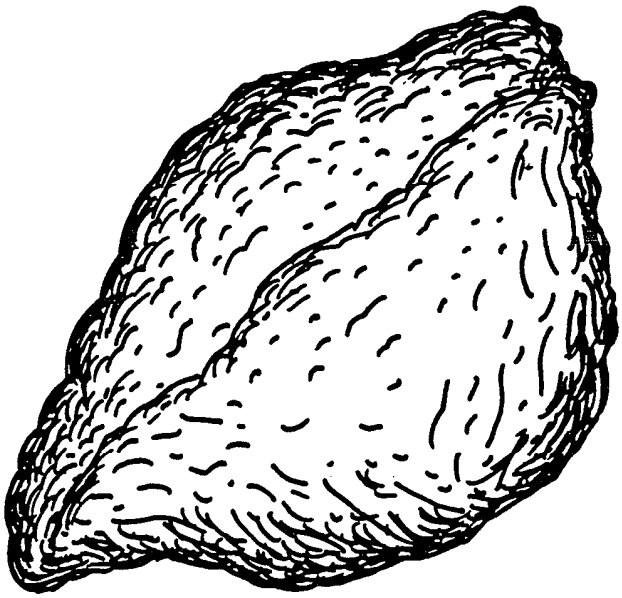
1. Wing



2. Drumstick



3. Thigh

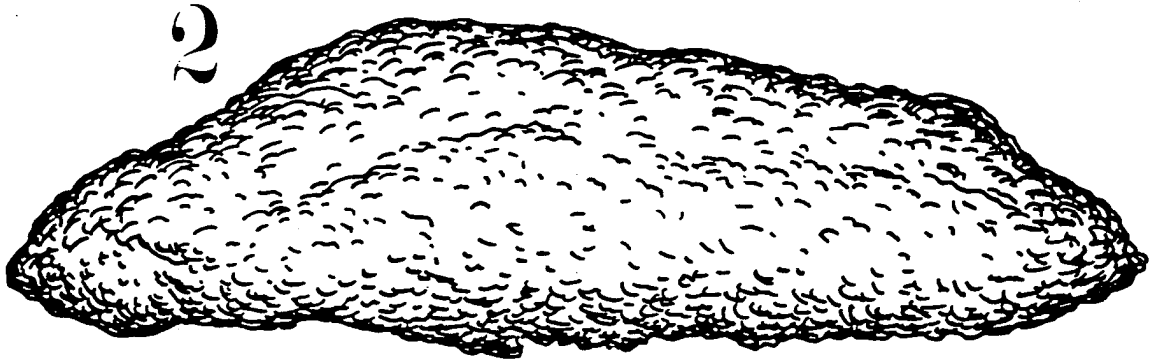


4. Breast

Fish

1

2



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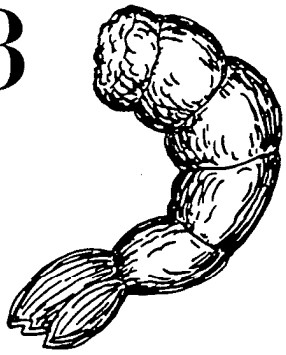
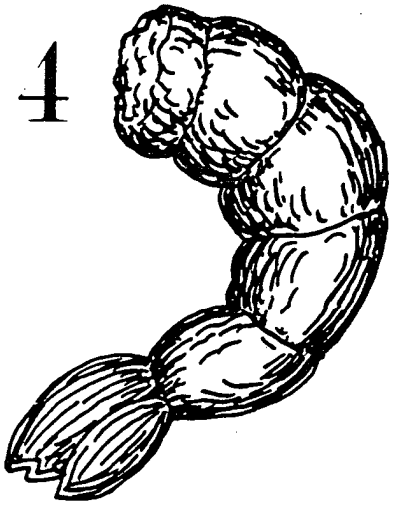


4



6.7.4. Guidelines for Instructing Subjects on the 24-hour Dietary Recall

(the following is a suggested "script" to use when talking to the patient/parent)

Trainer/Study coordinator: An important part of this research study is knowing what foods your child is consuming. In the next few weeks following this visit, you will be asked to participate in a series of three "dietary recall interviews" where our study dietitian will call and ask you questions in order to determine what your child had to eat and drink on the preceding day. You just need to answer the questions honestly and with as much detail as you are able to provide.

Trainer/Study coordinator: When reporting on what your child had to eat or drink, it is also important to know how much he or she consumed. Don't worry, we are not going to ask you to weigh and measure everything that he or she eats! Instead, we use common household measurement tools and units, as well as an illustrated portion guide, to help you estimate the amount of food or drink consumed.

Trainer/Study coordinator: Common household measurement tools include things like cups (or fractions of cups, for example ½ cup or 1/3 cup), teaspoons and tablespoons, fluid ounces for beverages, etc. You can use these terms to estimate a portion size. You are also encouraged to use food label information to provide portion sizes.

NEXT, SHOW THEM THE GUIDE

Trainer/Study coordinator: Here is our Food Portion Guide, which you may also use to estimate portions. But first, let's look through it together and I'll show you how we use it by going through some examples.

EXAMPLE 1: The dietitian asks you, "what was the first thing your child had to eat in the morning?" You reply "a bowl of oatmeal". The dietitian will ask you to turn to page 10 and look at the bowls there. Imagine they are actual size. Which bowl is closest to the bowl your child used for oatmeal? Let's say you reply "Bowl 3". Next, you will be asked how much of the bowl was filled with oatmeal. You reply "to line C". And that's it! You've estimated the amount consumed.

EXAMPLE 2: You report that your child had a brownie at 3pm for a snack. The dietitian will ask you to turn to page 1, "Squares and Rectangles", and ask you to picture the brownie placed on the page with the edges lined up to the lower left corner of the grid. Now, how big is the brownie using the numbers on the grid? You reply that the brownie fits into "square 12 by square 10".

6.7.4. Guidelines for Instructing Subjects on the 24-hour Dietary Recall

EXAMPLE 3: For dinner, you state that your child had a hamburger that was prepared at home. The dietitian will ask you to turn to page 2 and pick a circle that is closest to the size of the hamburger. You reply "circle E". We are halfway there. Next, the dietitian will ask you to turn to page 4 and look at the different thicknesses. How thick was the hamburger? You reply "thickness 14". We now have everything we need to estimate the size of the hamburger.

Trainer/Study coordinator: It may seem like this is a lot of detail to provide, but as you get used to the process it will become quite easy for you to estimate intake.

Trainer/Study coordinator: Do you have any questions?

Trainer/Study coordinator: Thanks for allowing me the time to review this process with you. Keep this guide in a handy location so that you can access it during the recall interviews.

6.8. Baseline and follow-up liver biopsy (SD and other forms)

Details of liver biopsy procedures, tissue banking, slide preparation, and shipment of slides to the DCC are discussed in the SOP Part IV, Liver Biopsy and NAFLD/NASH Histology Scoring System document.

- Baseline liver biopsy must be obtained within 120 days prior to randomization for all patients who have been found to be eligible for CyNCh with respect to all other criteria
- A follow-up liver biopsy should be obtained at the f52 visit for all patients enrolled in CyNCh
- Blood for serum and plasma banking may be drawn immediately prior to the liver biopsy, but cannot be obtained in the 72 hour period after a liver biopsy
- The MRI exam will ideally be scheduled as close to the time of the biopsy as feasible
  - Baseline MRI should be within 90 days of baseline biopsy and prior to randomization
  - Follow-up/post-treatment MRI should be no more than 6 weeks before and 12 weeks after the f52 visit biopsy
- A pregnancy test (for women of child-bearing potential) should be obtained prior to the liver biopsy and MRI exam

Forms

- Occurrence of liver biopsy(s) done before screening and occurrence of liver biopsy during screening are queried on the Baseline Medical History (BH) form
- Occurrence of a biopsy since the previous CyNCh visit is queried on the Follow-up Medical History (FH) form
- The Liver Biopsy Materials Documentation (SD) form must be completed to document the outcome of all biopsies obtained for CyNCh (screening and follow-up) with regard to availability of tissue for banking and stained and unstained slides for scoring and archiving
- If tissue was obtained for banking, the Liver Tissue Banking (LT) form must be completed.
- If the biopsy was done prior to or during screening, then the local CyNCh Study Pathologist must complete the Liver Biopsy Histology Worksheet (HW) and the Clinical Coordinator must complete the Liver Biopsy Histology Findings (HF) form
- Central scoring of biopsies, shipment of slides to the DCC, and shipment of frozen liver tissue in RNA*later*Solution® to the Biosample Repository must be documented on the Central Histology Review (CR) form
- The Histology Slide Transmittal Log (TS) form must be completed and accompany every shipment of slides sent to the DCC
- The Specimen Shipment Log (SS) form must be completed and accompany every shipment of frozen liver tissue to the NIDDK Biosample Repository

The pediatrician, the Study Pathologist, and the Clinical Coordinator must work together to accomplish these tasks and each complete their sections of the required forms. Considerable cooperation and close communication will be required to complete these tasks successfully.

6.9. Baseline and follow-up MRI (MR and other forms)

Details of MRI procedures, case report forms, and submission of data to the Radiology Reading Center (RRC) are discussed in the SOP Part VI, MRI Procedure Manual.

- Baseline MRI must be obtained within 90 days of liver biopsy and prior to randomization for all patients who have been found to be eligible for CyNCh with respect to all other criteria
- A follow-up MRI should be obtained no more than 6 weeks prior to and no more than 12 weeks after the follow-up liver biopsy at the f52 visit for all patients enrolled in CyNCh.
  - It is preferred that the MRI exam is done while the patient is still using the study drug.
  - This MRI should be the same time of day as the baseline MRI.
- The MRI exam will ideally be scheduled as close to the time of the biopsy as feasible.
- A pregnancy test (for women of childbearing potential) should be obtained prior to the liver biopsy and MRI exam.

DCC Forms - entered into the NASH CRN data system

- The **MRI Consent and Report form (MR)** must be completed by the study pediatrician/radiologist and coordinator to document the occurrence of an MRI procedure obtained for CyNCh (screening and follow-up) and transmittal of images to the RRC.

RRC Forms - submitted to the RRC via fax (619-471-0503) or email (liclark@ucsd.edu)

- **MRI Radiologist Report CRF** (see SOP VI Appendix B) is completed by the Study Radiologist after the images are reviewed. If there are any significant findings, the Study Pediatrician must be notified.
- **MRI Data Transmittal CRF** (see SOP VI Appendix A) is completed by the Clinical Coordinator
- **MRI Adverse Event CRF** (see SOP VI Appendix C) is completed by the Clinical Coordinator for each MRI that is performed, whether or not there are adverse events.

MRI Related Adverse Events

If there are adverse events related to the MRI procedure, the Clinical Coordinator should notify a Study Pediatrician and complete an Adverse Event (AE) form for the DCC. More information regarding adverse events is discussed in Section 6.17 Adverse Event Reporting.

The Study Pediatrician, Clinical Coordinator, Study Radiologist, and other Imaging Personnel must work together to accomplish these tasks and each complete their sections of the required forms. Considerable cooperation and close communication will be required to complete these tasks successfully.

6.10. Alcohol use questionnaires (AD)

What / Who

- AUDIT (AD) form
- Summary question on CyNCh Randomization Checklist (RZ) form
- Questions on interval alcohol consumption on Follow-up Medical History (FH) form
- Flash Card #9, Drink Equivalents, can be used with the alcohol questionnaires

Purpose

- At screening, obtain a detailed history of the patients alcohol consumption patterns from the onset of regular drinking
- Monitor alcohol use during follow-up

Who

- All CyNCh patients

How

- Form AD is self-administered for patients, without help from spouse or family

Comments

- At screening, the patient is never asked directly how much alcohol he/she drinks per week on average; clinic staff must judge this based on all information obtained from interview, chart review, discussions with those who know the patient etc; the clinic staff use their best judgement to answer the eligibility question on the CyNCh Randomization Checklist (RZ) form
- The Clinical Coordinator should complete section A on page 1 of Form AD and record patient ID on subsequent pages before asking the patient to complete the form

6.11. Quality of life questionnaires (PQ, PR, PW, PY)

Purpose

- To evaluate correlations between self-reported quality of life and disease severity

What / Who

- All CyNCh patients and parents

Forms

- PQ: Pediatric QOL: Parent Report for Teens, ages 13-17 (English or Spanish)
- PR: Pediatric QOL: Parent Report for Child, ages 8-12 (English or Spanish)
- PW: Pediatric QOL: Child Report, ages 8-12 (English or Spanish)
- PY: Pediatric QOL: Teen Report, ages 13-17, (English or Spanish)

When

- Visit s
- Follow-up visits f52 and f76

Procedure

- Clinical Coordinator should complete Part A and apply labels to subsequent pages as needed before giving the form to the patient to complete
- Self administered or by interview for patients and parent
- Clinical Coordinator should check returned forms for completeness before the family leaves the clinical center

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6.12. Laboratory measures (LS and LR)

Who

- All CyNCh patients

What

- Form Laboratory Results – Tests Done Only During Screening (LS) form covers assessments collected only at screening:
  - Screening etiologic tests
  - Iron assessments
  - Ceruloplasmin measurement
  - Alpha-1 antitrypsin assessment
  - Autoantibody studies

- Form Laboratory Results – Screening and Followup (LR) form covers assessments collected during screening and follow-up
  - Hematology
  - Chemistries
  - Prothrombin time, INR, and HbA1c
  - Liver panel
  - Fasting lipids
  - Fasting glucose
  - Pregnancy

When

- Form LS: Visit s
- Form LR: All visits
- Given the extent of information recorded on form LS, you may still be completing it at visit s2 or drawing blood for tests at visit s2; use visit code s anyway
- Requirements for fasting – nothing by mouth except water for at least 12 hours before blood draw

Instructions for Form LS

- Most of the tests on Form LS are intended to be obtained by chart review; time windows for the allowed age of tests are specified on the form
- Serological assessment to exclude viral causes of chronic liver disease is required for all patients
- Iron overload screening is required for all patients; hepatic iron index is recorded if available, but is not required
- Ceruloplasmin is required
- Alpha-1 antitrypsin assessment is required for all patients
- Autoantibody studies are required for all patients

Instructions for form LR

- The measures on form LR can also be obtained by chart review, both at screening and during follow-up; the time window for each type of assessment is specified on the form

6.12. Laboratory measures (LS and LR)

- During follow-up, the time window for the assessment is "in the time window for the follow-up visit (check the patient's Visit time window guide)" – e.g., f36 has an acceptable calendar time period within which it may be done; if you can find a hematology assessment in the patient's chart that was done under the same conditions as required by the study and which provides the required values and was done within the time window for visit f36, you do not need to order another hematology at f36
- If the chart review tests are out of the time window or the test conditions can't be ascertained or differ from what is required, the measures have to be done at the study visit and can be charged to the study
- For baseline, the required time window is within 90 days of the liver biopsy.
- All laboratory test results are required during screening.

6.13. Plasma and serum collection for Biosample Repository (BP)

Purpose

- Collection of whole blood from the CyNCh trial patients; when timed to coincide with a liver biopsy, blood should be collected ideally within ± 7 days and up to ± 90 days of the biopsy. Blood should not be collected in the 72 hour period after a biopsy
- Separation of plasma and serum at clinical center:
  - Screening visit, f12, f24, f36, f52, and f76: ten 0.5 mL aliquots of plasma and twenty 0.5 mL aliquots of serum are to be obtained in 2.0 mL cryogenic vials.
- Store plasma and serum aliquots at -70° C prior to batch shipping to the NIDDK Biosample Repository at Fisher BioServices

Fasting Instructions

- Patient instructed to fast 12 hours (recommended) prior to blood draw; an 8-hour fast prior to blood draw is allowable. *Note if the patient has not fasted a minimum of 8 hours at visits f04, f12 and f36, blood may still be collected for banking, please document this on the BP form item 8.

Forms / Materials

- BP - Blood Processing for Plasma and Serum
- Labels for heparin (green top) tube and serum separator SST tubes (red top)
- Labels for plasma and serum cryovials
- Barcode scanner
- SS - Specimen Shipment log and Excel Spreadsheet
- NIDDK Biosample Repository shipper

When

- Visit s
- Followup visits (f12, f24, f36, f52, f76)
- Batch shipments: Monthly or semi-monthly

By whom

- Phlebotomist
- Clinical Coordinator
- Person responsible for shipping to NIDDK Biosample Repository must have formal, documented training to package and ship hazardous goods, per DOT/IATA guidelines

6.13. Plasma and serum collection for Biosample Repository

Equipment

Blood tubes/aliquot vials

- One 10 mL sodium heparin (green top) tube - *provided by clinical center*s
- Two 10 mL SST (red-gray top) tubes - *provided by clinical centers*
- Up to thirty 2.0 mL cryogenic vials - *provided by clinical centers*
  - vials should be able to withstand -196 degrees C
  - vials should be self standing (flat bottom, not curved), externally threaded, 13.5 mm wide x 48.3 mm tall, with silicone washers

Labels

- Preprinted labels for whole blood collection tubes (10 mL heparin tube and 10 mL SST tubes) and preprinted labels for Form BP – *labels are printed at the clinical center via web-based data management system; use MACO ML-5000 1" x 1 ½" labels, 50 labels/page*
- Preprinted polypropylene labels for 2.0 mL cryogenic vials – *provided by the DCC*

Equipment

- Centrifuge
- -70° C freezer
- Swing out rotor
- 5 mL pipettes

Blood processing procedures

- Patient instructed to fast 12 hours prior to blood draw (recommended); an 8-hour fast prior to blood draw is allowable. *Note if the patient has not fasted a minimum of 8 hours at visits f04, f12 and f36, blood may still be collected for banking, please document this on the BP form item 8.
- Collect whole blood into one 10 mL heparin (green top) tube for plasma
- During visit s and f76, collect whole blood into two 10 mL SST (red-gray top) tubes for serum.
- During other follow-up visits, collect whole blood into one 10 mL SST tubes for serum.
- If sample appears to have hemolyzed, do not aliquot. Re-draw blood

Plasma

- Collect blood into heparin (green top; Becton-Dickinson) tube. Ensure that heparin tubes have not expired. (*check that date shown above "Exp" in lower right corner of label is later than current month*)
- Completely fill vacutainer tube
- Mix gently by inversion 5 times
- Within 30 minutes, centrifuge at 1800 x g for 15 minutes at 4° C, preferably with a swing out rotor
- Immediately after centrifugation, insert a 5 mL pipette below surface of plasma

- Remove the clear plasma while avoiding blood cells
- Transfer plasma into aliquots of 0.5 mL each into 10 labeled 2.0 mL cryovials
- Freeze at -70° C immediately
- Processing of plasma should be completed within 30 minutes

Serum

- Collect blood into serum separator (red-gray top) tubes. Ensure that SST tubes have not expired. (*check that date shown above "Exp" in lower right corner of label is later than current month*)
- After filling, invert each SST tube gently at least 5 times
- Allow blood to clot for **at least 30 minutes** at room temperature
- Centrifuge at 1800 x g for 15 minutes at 4° C, preferably with a swing out rotor
- Transfer 0.5 mL of serum into 10-20 labeled 2.0 mL cryovials
- Freeze at -70° C immediately
- Processing of serum should be completed within two hours

Note: Separated serum and plasma may be stored at -20° C for up to one day before transfer to -70° C while ensuring samples remain frozen during the transfer.

Blood Processing for Plasma and Serum (BP) form

- Complete the Blood Processing for Plasma and Serum (BP) form
- Affix labels for the heparin plasma and the SST serum to the BP form
- Affix aliquot 00 cryovial labels to the BP form

Shipping samples to the NIDDK Biosample Repository

- Specimens are to be batch-shipped monthly to Fisher BioServices on Monday, Tuesday, or Wednesday
- Aliquots will be stored locally at the clinical center at -70° C prior to shipping
- Ship specimens in the STP 320 Saf T Pak shipper (provided by the NIDDK Biosample Repository)
- Open the template Excel file used for shipments and scan each cryovial using the carcode scanner provided to your clinical center. The file should have the filename: NASHCRNsiteXXX_shipdate.xls. Replace the 'xxx' with your clinical center three digit site ID and replace 'shipdate' with the date of shipment
- The Excel shipping file has column headings for barcode number: Site ID-Patient ID numbers; 3 letter patient code; date collected; specimen type: plasma, sera, liver tissue; volume; units of measure; study number; and visit code
- Record the Federal Express Airbill tracking number, at top of page 3, of the Specimen Shipping Log.
- Complete Section A. Center ID, shipment and study information and section B. Clinical Administrative information of the Specimen Shipment Log (SS). Enclose a printed copy of the Specimen Shipment Log and the Excel spreadsheet with each shipment of specimens.

- Keep a notebook of all original completed Specimen Shipment Logs (Form SS) and Excel spreadsheet so that you have a record of all shipments to the Biosample Repository
- Notify the Biosample Repository of the shipment via fax (301-515-4049) or email bio-niddkrespository@thermofisher.com) on the day the package is picked up by Federal Express. Include the tracking number in the subject line of the email.

Packaging Procedures

- Check that 1 absorbent pad is in the Saf T Pack Bio hazard plastic bag
- Insert frozen cryovial into small cardboard boxes with dividers. Place only one tube into each cardboard cell. Each cardboard box may hold 81 cryovials
- Insert each cardboard box with cryovials into its own plastic bag and seal
- Place each plastic bag with specimen box into its own STP-710 Tyvek envelope and seal.
- Place each Tyvek envelope into STP-111 inner brown cardboard box. No more than 3 Tyvek envelopes containing boxes with cryovials can be placed into the STP-111 inner brown cardboard box. If shipping only 1 or 2 specimen boxes, fill the rest of the space inside the cardboard inner box with bubble wrap to prevent movement
- Tape the inner cardboard box closed before placing the styrofoam cooler
- Place cardboard box in upright position in bottom of styrofoam cooler
- Surround the STP-111 inner brown cardboard box with abut 8 kg of 2" blocks or nuggets of Dry Ice
- Fill excessive room left in the insulated freezer box with bubble wrap to stabilize specimens in transit
- Place the polystyrene lid onto the freezer box
- Place the “Empty Packaging” cover and shipping form, with Excel spreadsheet on the top of the cooler lid
- Place a completed Specimen Shipment Log (Form SS) on top of the cooler lid
- Close and seal outer cardboard box with tape

Labeling Shipper:

- Place a checkmark in the block on the outer cardboard box next to “BIOLOGICAL SUBSTANCE, CATEGORY B”. Do not cover this marking with labels.
- Affix a label with your name and return address to the side of the box in the “Shipper:” block
- Affix the repository address label to the side of the box in the “Consignee:” block
- Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms
- Affix the “UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B” label to the right of the dry ice label
- Use the preprinted Federal Express air bill to ship specimens to the NIDDK Biosample Repository. Complete return address (leave “Sender Federal Express account number” blank). Section 6, Special Handling: Check “Yes, Shippers Declaration not required,” check “Dry Ice” block and entry “1” x “8” kg. Section 7, Enter “1" under “Total Packages” and the total weight of 24 lbs. Place completed Federal Express Airbill on side of box adjacent to the labeled side. Call Federal Express at 1-800-463-3339; give them the account number in section 7 of the Airbill

  Do not write on exterior of box

  Do not ship frozen packages on Friday; the repository is closed on weekends

6.14. Symptoms of Liver Disease (LP)

The symptoms of Liver Disease (children) form is designed to document participant-reported symptoms associated with liver disease. See form: LP-Symptoms of Liver Disease, for additional information associated with how the LP form is administered and the symptoms queried.

6.15. Genetic consent and blood collection documentation (CG)

Purpose

- Collection of whole blood from CyNCh patients who consent for genetic research
- Shipment of whole blood to the NIDDK Genetics Repository at Rutgers University for DNA banking
- Do not repeat genetic consent or blood draw for patients who have had blood drawn for genetic research as part of other NASH CRN studies, unless original yield was low.

Forms

- CyNCh consent for genetic research
- Genetic Consent and Blood collection Documentation (CG) form
- NIDDK Genetics Blood Collection form

When

- Visit s (or as needed during follow-up due to a low yield [less than 50g] of DNA)
- Ship same day as whole blood collection

By whom

- Clinical Coordinator and Study Physician (to obtain consent)
- Phlebotomist (to obtain whole blood)
- Person responsible for shipping whole blood to NIDDK Genetics Repository must have formal, documented training to package and ship hazardous goods, per DOT/IATA guidelines

Equipment

- Two 10 mL NaEDTA vacutainer tubes (purple top) - *provided by NIDDK Genetics Repository*
- Preprinted whole blood tube labels and form CG labels - *provided by clinical centers (printed from web based data management system; clinical center provides MACO ML-5000 labels (1" x 1 ½ ", 50 labels per page, www.maco.com)*
- Shipper - *provided by NIDDK Genetics Repository*
  - One model 472 Thermosafe Safety Mailer (body and lid)
  - One 2 ½" x 9" pre-cut section of absorbent materials
  - Two 18" strips of red waterproof tape
  - One press-lock plastic bag
  - One corrugated shipping carton with locking tabs
  - One pre-printed Fed Ex airbill with third party billing
  - One NIDDK Genetics Blood Collection form
  - Instructions for Blood Sample Collection form

6.15. Consent and specimen collection for Genetics Repository (CG)

Blood collection procedures

- Affix MACO tube label onto the tube and avoid covering the barcode label
- Collect blood into two 10 mL NaEDTA (purple top) tubes
- Invert each tube gently 6 times to mix blood with additives
- Keep blood at room temperature
- Check that patient ID information on preprinted tube labels matches information recorded onto the NIDDK Genetics Blood Collection form

Packaging procedures

- Ship whole blood at ambient room temperature same day to the NIDDK Genetics Repository
- Package the whole blood tubes in the body of the Safety Mailer (Model 472 Thermosafe Safety Mailer)
- Place absorbent material so it exactly covers cavity of the Safety Mailer
- Place lid of Safety Mailer over body and absorbent material and press down firmly so that lid closes properly. Reposition absorbent material so that it does not get caught between the lid and body
- Peel backing from two 18" long pieces of red waterproof tape and seal the Safety Mailer lid to the body; peel backing from second piece of tape and continue sealing the mailer, overlapping the first piece of tape about two inches on both ends
- Place the sealed Safety Mailer into the press-lock plastic bag. **Do not seal the bag**.
- Place the NIDDK Genetics Blood Collection form in the mailer box outside the plastic bag
- Slide the Safety Mailer and open press-lock bag into the corrugated carton
- Seal the press-lock bag and close carton using the locking tabs
- Place sealing tape (not included) over them

Shipping procedures

- Use the preprinted Federal Express shipping label, marked for *Priority Overnight Delivery*, to ship whole blood to the NIDDK Genetics Repository
- Outside cardboard box must have stamped “Diagnostic Specimen Packed in Compliance with IATA Packing Instructions 650"
- Call Federal Express, 1-800-Go-FEDEX (1-800-463-3339) for courier*
- Notify Dana Witt-Garbolino or Dale Heyward at the NIDDK Genetics Repository that blood is being shipped and provide the Federal Express tracking numbers and the NIDDK ID numbers. Notification may be via:
  - Web portal: http://rucdr.rutgers.edu/shippingblood
  - email: witt@biology.rutgers.edu
    Heyward@dls.rutgers.edu
  - Fax: 1-732-445-1149
  - Telephone: 1-732-445-1498

- Ship whole blood to:
  Rutgers University/Cell Repository/NIDDK
  604 Allison Rd., Room C120A
  Nelson Laboratory
  Piscataway, New Jersey 08854-8000

- Do not schedule deliveries the day before or the day of a national holiday. Check with Federal Express and with the Genetics Repository if there are any questions about delivery availability or closure.

Genetics Repository Web Portal System
Rutgers University Cell and DNA Repository - (RUCDR) implemented Laboratory Information Management System (LIMS) software to track shipments. **Please note that the system is not compatible with Mac systems.**

- Please call 732-445-4429 with ANY questions about computer configuration for immediate support. The list of requirements are posted here: https://rucdrlims.rutgers.edu/starlims10.rucdrlims/support/default.htm

- Additionally, they have set up a support email account to specifically address LIMS questions. The address is starlimshelp@biology.rutgers.edu.

Establishing a Username and Password

http://rucdrlimsregister.rutgers.edu/

- Go to the URL listed above and then just follow the directions on the page. You will receive a confirmation email. You will then be contacted to establish your account.

Training videos

- There are training videos for several functions on their website: http://www.rucdr.com/training.htm
- **RUCDR STARLIMS Request for Supplies** (http://rucdrlimstraining.rutgers.edu/reqsupply_video.htm)

This video tutorial will teach you how to order supplies such as collection kits, phlebotomy forms and FedEx AirBills through the RUCDR STARLIMS system. The video will guide you through the appropriate steps of requesting supplies from the RUCDR. Should you need any additional help after watching the video, please contact our RUCDR STARLIMS helpdesk by phone at 732.445.4429 or email at starlimshelp@biology.rutgers.edu.

- **RUCDR STARLIMS Sample Submission** (http://rucdrlimstraining.rutgers.edu/presubmission_video.htm)

This video tutorial will teach you how to preregister your samples through the RUCDR STARLIMS system. By watching the video, you will learn the steps required to correctly preregister your samples before they are sent to the RUCDR.

Logging in to the System

- The URL for the RUCDR StarLIMS system is https://rucdrlims.rutgers.edu/starlims10.rucdrlims/start.lims Enter your username and password. If you ever forget your username or password there are options on this screen to retrieve a lost password or username. You will need to remember what email address you used to create your account to use this function!

Sample Submission

- Use the STARLIMS system to notify the NIDDK Genetics Repository that blood is being shipped and provide the Federal Express tracking numbers and the NIDDK ID numbers. Notification may be via:
  - STARLIMS system: https://rucdrlims.rutgers.edu/starlims10.rucdrlims/start.lims
  - Fax: 1-732-445-1149
  - Telephone: 1-732-445-1498

Self Help Resources

- This tab is a holding area for useful documents.

1. **FAQ** – If you have a question, hopefully it is already answered here.
2. **Download Center** – These instructions are here! Also, any paperwork enclosed with mailer kits is here in case you need to print off extras.
3. **View Announcements** – In case you missed the announcement page when you first logged in to the web portal you can read it again.
4. **Support Resources** – Links that may be of interest to visit.

Account Management

- From this tab you can "Modify Your Profile" or "Change Password".

Important Information Regarding Blood Shipments

- When a package is received, a mailer request is filled or a question is answered, you will receive an email from us and the status will be changed to "closed".

6.16. Study drug dispensing and return (DD and RD)

Forms

- DD - Drug Dispensing Documentation form
- RD - Study Drug Dispensing and Return form

Drug supply

- Cysteamine Bitartrate Delayed-Release: 75 mg/capsules, (150 count bottle) taken orally in the morning and the evening 30 minutes prior to meals
- Placebo: 75 mg capsules taken orally twice a day (qd)

Dispensing of study drug

- Study drug to be dispensed to participants at: Rz, f04, f12, f24 and f36 visits
- 3 month supply (3 bottles)
- Do not attempt to "re-use" bottles of study drug already dispensed to the patient, always collect all study drug bottles at each visit, and dispense new study drug bottles.

Checks on return of study drug

- Unused study drug to be returned by patient at: f04, f12, f24, f36, f52 and f76
- Children and parents should be reminded to return empty and partially used study drug bottles at all followup visits

Procedures at clinical center

- The DD form must be keyed at each followup visit to receive the bottle numbers to be dispensed to the patient; the DD form may be completed and keyed prior to the visit so the study drugs can be ordered from pharmacy
- The RD form **must be keyed within 48 hours of dispensing study drug to the participant** to document the capsules and bottle numbers returned as well as the bottle numbers dispensed at each visit

By whom

- CyNCh clinical coordinator or pharmacist

Ordering procedures at clinical center

- Inventory current drug supplies
- Study drug supplies are shipped to arrive within 2 working days of receipt of order
- Notify DCC if the supply falls below 30 bottles

Handling and disposal

- Unused portions of open bottles in the possession of patients should be considered contaminated and handled accordingly

6.16. Study drug dispensing and return (DD and RD)

- Returned capsules should be counted by the pharmacist and/or clinic coordinator and the number of capsules and the number bottles returned, should be recorded on the RD form and the CyNCh Trial Drug Accountability Record
- Expired study drug, partially used study drug, and bottles of study drug returned by patients may be destroyed following your institution's procedures for disposal of investigational study drug once the CyNCh Trial Drug Accountability Record has been audited and approved by the Data Coordinating Center
- Documentation should be recorded onto the CyNCh Trial study drug accountability records to account for all returned study drug as well as its destruction per your institutional guidelines

Storage and stability

- Store at room temperature (68-77 degrees F) in a cool dry place

6.17. Adverse event reporting

Definitions (21 CFR 312.32 IND Safety Reporting). To access CFR 312.32 IND Safety Reporting click on:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Reportable CyNCh adverse events

- Adverse events should be recorded on the CyNCh Adverse Event Report (AE) data form whether or not thought to be associated with CyNCh or the study drug.
- Any event threatening the integrity of the CyNCh Trial or well-being of the participant (e.g., suspected fraud) is a reportable event. We recognize that this category is not well-defined; however, it is included as a reminder that reportable events can have a broader scope than events that happen to a patient. Some examples include:
  (1) events that impact the patient's treatment or participation in CyNCh;
  (2) adverse events that are recorded on the Follow-Up Medical History (FH) form;
  (3) adverse events that may or may not be related to study drug;
  (4) other events that clinical center staff feel should be reported;
  (5) when a follow-up report is needed for a previously completed Adverse Event (AE) form.
- Deciding whether an event is reportable to CyNCh (i.e., is in either of these categories) will be the responsibility of the Principal Investigator of the clinical center.

- The Data Coordinating Center will maintain a list of adverse events for reporting and review at Steering Committee meetings and DSMB meetings.

CTCAE v3.0

- The NASH CRN uses the Common Terminology Criteria for Adverse Events, (CTCAE v3.0) to specify and grade adverse events.
- This document is posted on the NASH CRN website (www.nashcrn.com – click on Studies and then click on CyNCh)
- Use the CTCAE v3.0 to specify the Short Name for the adverse event and the severity grade for the adverse event. All adverse events should be assigned a severity grade 1-5.
- Adverse events Grade 3 or higher must be faxed to the DCC within 1 week for immediate review by the Safety Officer, Dr. Jeanne Clark.

Local reporting requirements

- Your clinical centers' IRB has reporting requirements of its own regarding events occurring in the course of conduct of a study. These reporting requirements may be more stringent than those adopted by CyNCh. Regardless of what CyNCh requires, you must continue to meet your local IRB's requirements. If the local requirements are more stringent than CyNCh, you may report events locally that you do not report to CyNCh.
- It is possible that some CyNCh patients will develop significant liver-related morbidity or mortality during the course of followup. This information is important and should be documented on the Followup Medical History (FH) form and Adverse Event Report (AE) data form, but it may also be considered a reportable adverse event according to the local institutional guidelines.
- For more information please refer to FDA Guidance for Clinical Investigators, Sponsors, and IRB: Adverse Event Reporting to IRBs – Improving Human Subject Protection: https://jhuccs1.us/nash/closed/ctprot/CyNCh/GuidanceAEreporting.pdf

6.18. Serious adverse event reporting

Definitions (21 CFR 312.32 IND Safety Reporting)

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered **"SERIOUS"** if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the CyNCh study drug caused the adverse event. For the purposes of IND safety reporting**, "REASONABLE POSSIBILITY"** means there is evidence to suggest a causal relationship between the CyNCh study drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered **"UNEXPECTED"** if it is not listed in the most current cysteamine bitartrate brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Expedited review process

- Adverse events that are judged by the principal investigator to be **SERIOUS**, **UNEXPECTED** and have a **REASONABLE POSSIBILITY** of being caused by CyNCh study drug should be recorded on the Serious Adverse Event/IND Safety Report (SR) form. The SR form should be entered into the data system and faxed to the DCC within 2 business days along with a narrative of the event and a copy of the clinical center's IRB report.

- The narrative should describe the serious adverse event and include History with the CyNCh study drug, any comorbidities, concurrrent medications with doses, and any recent changes hospitalizations or ER visits and justification of how the serious adverse event is determined to be serious, unexpected, and have reasonable possibility of being caused by CyNCh study drug as defined above and in 21CFR312.32.
- The Data Coordinating Center along with the Safety Officer, Dr. Jeanne Clark, will review the materials to make sure that the required information is included. At any time, the DCC may ask for revisions of the supporting documentation and further clarification of the serious adverse event until the amount of information is sufficient.
- The DCC will notify NIDDK of the event within 3 business days of receiving the SR form and submit a preliminary report for further review of the material. At any time NIDDK may ask for additional information or further clarification of the serious adverse event.
- Not every SR form that is submitted will result in an expedited IND Safety Report to the FDA. The final decision will be the responsibility of the NIDDK (sponsor).
- If NIDDK determines that the serious adverse event requires an expedited IND Safety Report, they will notify the FDA within 7 business days of the SR form receipt at the DCC.
- Within 1 month of the initial SR form, the clinical center must submit to the DCC and the NIDDK a follow-up report when:
  (1) serious adverse event is resolved;
  (2) there has been a significant change in the patient's condition;
  (3) in the physician's judgment about the serious adverse event (and periodic updates if needed) to report the details of the disposition of the serious adverse event.
- For more information, please refer to the FDA Final Rule: IND Safety Reporting requirements for Human Drug and Biological Products: http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf

Data Coordinating Center responsibilities

- The Data Coordinating Center will catalog all serious adverse events for reporting and review at Steering Committee meetings and DSMB meetings.
- The DSMB will review each serious adverse event report and provide comments to the NIDDK project officer and Steering Committee. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the serious adverse events and recommend any actions to the NIDDK.
- If the FDA determines that a change to the investigators brochure, IND or protocol is needed, the Data Coordinating Center will send a copy of the report to all clinical centers, with instructions to forward the report to their IRB. Copies of the report will also be sent to the NIDDK, Data and Safety Monitoring Board (DSMB).

6.18. Serious adverse event reporting

Local reporting requirements

- When you receive a report from the Data Coordinating Center regarding occurrence of an event reportable to the CyNCh trial at another NASH CRN clinical center, you must forward that report to your IRB. It may be that your IRB has no comment on events occurring elsewhere; nevertheless, the notification of your IRB is still a CyNCh requirement.
- Your clinical centers' IRB has reporting requirements of its own regarding serious adverse events occurring in the course of conduct of a study. These reporting requirements may be more stringent than those adopted by CyNCh. Regardless of what CyNCh requires, you must continue to meet your local IRB's requirements. If the local requirements are more stringent than CyNCh, you may report events locally per your IRB guidelines.
- For more information, please refer to the FDA Guidance for Clinical Investigators, Sponsors, and IRB: Adverse Event Reporting to IRBs – Improving Human Subject Protection: https://jhuccs1.us/nash/closed/ctprot/FLINT/GuidanceAEreporting.pdf

6.19. Anticipated adverse events

Essentially all children with NAFLD have metabolic syndrome or overt, previously diagnosed or undiagnosed Type 2 diabetes. Furthermore, advancement of metabolic syndrome and diabetes and emergence of the multitude diabetic complications are typically gradual, ongoing processes. Please consult the cysteamine bitartrate brochure for a complete and current listing of anticipated adverse events: https://jhuccs1.us/nash/closed/cped/CYNCH/InvestigatorBrochure_13Jan12.pdf.

Cardiovascular, Cerebrovascular, and/or Peripheral Vascular:Angina, atherosclerosis, acute coronary syndrome, cardiac ischemia, myocardial infarction, cerebrovascular accident (CVA) or stroke (ischemic or hemorrhagic), cerebral ischemia, transient ischemic attack, claudication, decreased peripheral pulses, and abnormal ankle-brachial index.

Dermatologic: Acanthosis nigricans, foot ulcers, and stasis ulcers.

Endocrine: Hypo- and hyperglycemia, elevated hemoglobin A1C, insulin resistance, dyslipidemia, ketoacidosis, and hyperosmolar hyperglycemia.

Gastrointestinal: Gastric and intestinal dysmotility (related to autonomic neuropathy) and mesenteric ischemia (intestinal atherosclerosis).

Immunologic/Infectious: Infections including foot infections, urinary tract infections (including fungal infections and emphysematous urinary tract infections), superficial fungal infections (oral and/or esophageal candidiasis, onychomycosis, candidal intertrigo, and vulvovaginal candidiasis), zygomycosis (mucomycosis), malignant (necrotizing) external otitis, pyomyositis (primary bacterial infection of skeletal muscle characterized by the formation of one or more intramuscular abscesses), and necrotizing infections of the skin and fascia (which may necessitate surgery and amputations).

Neurologic: CVAs. Diabetic neuropathy and related signs and symptoms including numbness, tingling, decreased sensation, neuropathic pain, and sensory or autonomic neuropathy.

Ophthalmic: Diabetic retinopathy and related signs and symptoms including nerve-fiber layer infarcts (cotton-wool spots), intraretinal hemorrhages, hard exudates, retinal microvascular abnormalities (including microaneurysms, occluded vessels, and dilated or tortuous vessels), macular edema, macular ischemia, neovascularization, preretinal and vitreous hemorrhage (with or without subsequent fibrosis), and traction retinal detachment. Acute and/or chronic vision loss related to diabetic retinopathy may also occur.

Orthopedic: Charcot foot, bony infarcts, and amputations secondary to these complications, ulcers, or peripheral vascular disease.

6.19. Anticipated adverse events

Renal: Diabetic nephropathy and related signs and symptoms including micro- and macroalbuminuria, proteinuria, glucosuria, ketonuria, glomerular hyperfiltration, mesangial expansion, glomerular basement membrane thickening, and nodular glomerulosclerosis (Kimmelstiel-Wilson lesions). Acute and/or chronic renal failure (characterized by rising serum creatinine and BUN levels and/or electrolyte disturbances) and acute and/or chronic worsening of hypertension related to diabetic nephropathy may also occur. These complications may necessitate renal dialysis and renal transplantation

If such an event occurs, appropriate medical care should be provided immediately in the clinic. If a suspected anticipated event is reported by telephone at the time of the event or later, the participant should be evaluated in the clinic by medical staff or referred to an appropriate facility for evaluation and management.

6.20. Procedures for unmasking treatment assignment

- Treatment assignments are unmasked after all data collection for the CyNCh trial has been completed (i.e., after completion of the 24 week post trial followup for all patients)
- Unmasking of study drugs will occur under the following conditions:
  - **Severe allergic reaction (Stevens-Johnson Syndrome)**: Study drugs will be stopped indefinitely. The patient, primary care provider (PCP), local principal investigator and pharmaceutical manufacturer may be unmasked.
  - **Pregnancy during the study**: Study drug will be stopped indefinitely, and the coded medication will be unmasked. The patient, PCP, and investigator will be notified of the assigned treatment and the associated risks of teratogenicity.
- In unforeseen situations where the clinical center principal investigator considers unmasking is in the best interest of the participant's health and well being, unmasking may be done after notifying the Executive Committee.
- The Data and Safety Monitoring Board will review all instances of unmasking that occur.

6.21. Procedures for missed or incomplete visits (MV)

Purpose

- Record data about missed or incomplete visits

Form

- Missed or Incomplete Visit (MV) form

When

- At close of a visit window for any missed follow-up visit or for any follow-up visit with specific forms not completed

By whom

- Clinical Coordinator

Procedures for missed or incomplete in-person visits

- For a missed visit:
  - Date of missed visit is the last date of the visit window
  - Indicate reason(s) for missed visit
- For an incomplete visit:
  - Date of incomplete visit is the date on which a partial set of procedures was performed
  - Indicate reason(s) for missed procedures

6.22. Procedures for patients lost to follow-up

Purpose

- Ascertain vital status of patient
- Document reason(s) patient did not attend visit
- Ascertain if patient is lost to followup

When

- Whenever patient misses a study visit and is difficult to contact

By whom

- Clinical coordinator

Search strategies

- Contact all persons identified on the Patient Location (PL) form
  - Telephone different times during the day/evening
  - Send letter via regular or certified registered mail to determine if patient is still at listed address
- Check current telephone directory for listings both for the patient and the patient's contacts specified on the PL form, e.g., next of kin, health care professionals
- Check post office for forwarding address; ask patient's contacts for forwarding address
- Check obituaries
- Check state vital records

6.23. Procedures for mortality closeout (DR)

Purpose

- Record participant death

Forms

- Complete the Death Report (DR) form

By whom

- Study Physician and Clinical Coordinator

6.24. Medical management of patients and side effects

To keep recommendations and care for participants in the study as uniform as possible, investigators should generally discuss with participants what is laid out in the CyNCh SOP V: Standards of Care Documents for Pediatric patients with fatty liver disease.

Diabetes

Since patients with diabetes may be entered into the CyNCh trial, is is likely that some will develop diabetic-related events. The criteria for diabetes is as follows (Diabetes Care, January 2010, 33: S11-S61):

- Fasting blood glucose test: ≥126 mg/dL (7.0 mmol/L)
- Blood glucose level ≥ 200 mg/dL (11.1 mmol/L) after two hour OGTT (75 g load)
- Hemoglobin A1c measurement ≥ 6.5%

Few adverse events related to study drugs are expected. The most common side effects are abdominal pain, nausea, vomiting, anorexia (loss of appetite), fever, diarrhea, drowsiness, and rash. These side effects will often get better within a couple of weeks of starting cysteamine. Other potential adverse events are those related to blood draws, liver biopsy and MRI procedures. If such an event occurs, appropriate medical care should be provided immediately in the clinic and documented in the study chart.

6.25. Closeout and transferring into NAFLD Pediatric Database 2 Study (CO)

Purpose

- To close out a patient's participation in CyNCh and document the patient's consent to join or re-enter the the NAFLD Pediatric Database 2

Form

- Closeout (CO) form

When

- The Closeout form should be completed at the f76 visit or at the close of the f76 window for all patients randomized in CyNCh.

By whom:

- Clinical coordinator

Instructions

- Ask the patient if he/she consents to re-entering or enrolling in the NAFLD Pediatric Database 2

- Patients willing to re-enter or join the NAFLD Pediatric Database 2 should sign the most recent version of the NAFLD Pediatric Database 2 informed consent approved by your IRB (follow your institutional IRB guidelines for re-consenting participants previously enrolled in the NAFLD Pediatric Database 2.

- Each consenting patient should be scheduled for a NAFLD Pediatric Database 2 follow-up visit approximately 12 months after the date of their CyNCh f76 visit. For patients previously enrolled in the NAFLD Database 2, consult the patient's CyNCh visit schedule (time windows guide) generated at their enrollment and schedule the NAFLD Pediatric Database 2 visit that is open 12 months from the date of their CyNCh f76 visit.

- For patients who were not previously enrolled in the NAFLD Pediatric Database 2, a new NAFLD Pediatric Database 2 visit schedule (time windows guide) will be automatically generated when the CyNCh Closeout form (CO) is keyed into the online database. The new visit schedule will use the CyNCh randomization date as the effective date of enrollment into the NAFLD Pediatric Database 2. Schedule the participant approximately 12 months from their CyNCh f76 visit for their t144 NAFLD Pediatric Database 2 follow-up visit.

- For CyNCh participants who decline to participate in the NAFLD Pediatric Database 2; inform them that the study results and their treatment assignment will be available to them sometime after the close of the CyNCh trial.

7. Forms management

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7.1. Clinical center ID codes

Alphabetic IDs

- Alphabetic clinic IDs are used on forms, lists, and tables.
- Alphabetic clinical center IDs are based on the name of the institution with which the clinical center is affiliated.
- Assigned IDs:

Cincinnati Children's Hospital	CINC
Columbia University	CU
Northwestern Univ: Children's Memorial Hospital	NWU
Indiana University	IU
Saint Louis University	SLU
Baylor University: Texas Children's Hospital	BCM
University of California, San Diego	UCSD
University of California, San Francisco	UCSF
Univ of Washington: Seattle Children's Hospital	UW
Emory University	EU

Numeric site IDs

- The NIDDK Genetics and Biosample Repositories use numeric IDs to identify the NASH CRN clinical centers.
- These will be used on the specimens (whole blood and plasma, serum, and liver tissue samples sent to the Genetic and Biosample Repositories, respectively).
- Assigned IDs (satellite centers should use site ID of parent clinic):

Cincinnati	220
Columbia University	828
NWU	222
Indiana University	221
Saint Louis University	223
University of California, San Diego	224
University of California, San Francisco	225
Emory University	227

7.2. Patient identifiers

What

- Patient ID number
- Patient code

Patient ID number

- 4 characters, all numeric
- ID number labels will be distributed to clinics by the Data Coordinating Center
- The ID number for a patient will remain the same for the duration of the NASH CRN, even if the patient enters another NASH CRN study or if the patient fails screening and is subsequently re-evaluated – the ID never changes

Ranges of patient IDs assigned to clinics

Case Western Reserve University	CWRU/CCF/CINC	1001	-	1999
Columbia University	CU	9001	-	9999
Duke University	DUKE/NWU/JHU	2001	-	2999
Indiana University	IU	3001	-	3999
Saint Louis University	SLU/BCM	4001	-	4999
University of California, San Diego	UCSD	5001	-	5999
University of California, San Francisco	UCSF	6001	-	6999
Virginia Mason Medical Center	VMMC/UW	7001	-	7999
Virginia Commonwealth University	VCU/MSCH/EU	8001	-	8999

Patient code

- 3 character alpha code assigned by the Data Coordinating Center and printed on the ID number label
- Each patient code is unique across the NASH CRN

7.3. Visit ID code

- 1 to 3 character alpha-numeric code
- Determined by purpose of visit and timing with respect to visit windows
- Visit ID codes

s	Screening visits
Rz	Randomization
f04	4 weeks follow-up visit (approximately 1 month)
f12	12 weeks follow-up visit (approximately 3 months)
f24	24 weeks follow-up visit (approximately 6 months)
f36	36 weeks follow-up visit (approximately 9 months)
f52	52 weeks follow-up visit (approximately 12 months)
f76	76 weeks follow-up visit (approximately 24 months)
n	Unscheduled visit

7.4. General guidelines for forms completion

Ink

- Forms should be completed in blue or black ink that is dark enough to photocopy legibly.

Changing responses on forms

- If an error is made on the form, correct the response by marking through the response with one or two lines and writing the correct response next to or above the original response. The staff member making the correction should put their initials and the date in the margin by the correction. A brief explanation for the change should also be written in the margin; e.g., 'error', 'pt changed mind', 'wrong response checked'.
- Do not obliterate, erase, or white-out incorrect responses.
- The idea is to preserve an audit trail of the original response and subsequent changes to it.

Multipage forms

- The patient ID number should be written on the top right of every page of every form in the space provided -- protect yourself against ineffective staples and photocopying mishaps.

Miscellaneous

- All written responses should be printed legibly so the responses can be keyed to the database.
- Do not use abbreviations or short-hand that may not be easily understood or keyed in the written responses.
- Numeric data should be recorded in the units prescribed on the form and to the level of precision (number of digits) indicated on the form.
- All numbers should be right justified and leading and trailing zeroes should be recorded on the form where applicable (e.g., an age of 8 would be written and keyed as "08").
- All letter codes should be left justified with the remaining spaces left blank (e.g., a visit ID for the s visit code would be completed and keyed as "s").
- The clinical coordinator should review all responses for completeness and accuracy before signing off on the form.
- Wherever possible, forms should be completed in real time. Interviews and questionnaires should be completed on the actual data form.
- The data on some forms, such as the Laboratory Results form, will be transcribed from worksheets or lab reports, but the visit date on the form should correspond to the date the testing took place.
- Staple relevant lab reports and worksheets to the data form; if your lab reports are transferred to you electronically, print a paper copy of the report and staple the copy to the form.

Calculations

- All calculations should be performed using a calculator.
- Values should be rounded according to the NASH CRN data rounding rule (see section on data rounding rule, later in this chapter of the SOP).

7.5. Instruction box

- Each form includes an instruction box at the top of the first page. This instruction box gives the purpose of the form, when it should be completed, who administers the form, the respondent, and specific instructions for the form.

7.6. Form skips, stops, ineligibility symbols

Skip pattern

- Form navigation (skip pattern) instructions are indicated in **boldface**. Skips are designated by an arrow from that response to a box with the number of the next item to be completed.

Caution sign

- Cautions are designated by a triangle with enclosing a C

Stop sign

- Stops are indicated with an arrow from the response to a stop sign – instructions are given that must be fulfilled in order to continue with the form. For example, Form RG (Registration) asks if the patient has signed the consent form; if the response is "no", the form is stopped with the instructions that *'the consent form must be signed prior to continuing with screening'*.

Ineligibility sign

- Ineligible conditions are designated by an arrow from the response to the symbol:

Other

- Other special instructions are indicated on the form in *italics*. Some examples are:
  – *check only one*: only one of the listed responses should be checked
  – *check all that apply*: one or more of the listed responses may be checked
  – *specify*: a response should be printed on the line(s) provided

7.7. Headers and footers

- Data Collection Forms include headers and footers at the top and bottom of each page, respectively, which identify the form and the patient. The top right of the first page of each form has a space to check when the form is keyed [( )keyed]. The top right of subsequent pages is reserved for the patient ID number. The footers include the form abbreviation, form revision number and date, the form name, and the page number. For example:

CyNCh Patient ID: __ __ __ __

Form RG CyNCh
Revision 1 (07Jan11) RG - Registration Page 2 of 3

- The keyed box should be √ed when the form is keyed; the person keying the form should also date and initial the form by the keyed box.
- The patient ID number should be written on each page of the form.

7.8. Key fields

- The first 7 items of each form include the key fields which identify the clinical center, patient, visit and study

A. Clinical center, patient and visit identification
   1. Center ID: __ __ __ __
   2. Patient ID: __ __ __ __
   3. Patient code: __ __ __
   4. Date form completed: __ __ - __ __ __ - __ __
      day mon year
   5. Visit code: __ __ __
   6. Form & revision: __ __ __
   7. Study: CyNCh 8

- The form and revision number will be printed on the forms in item 6; if a form is only used for one specific visit, the visit code will also be printed on the forms.
- When a form revision affects the data that are collected, the form revision number and date will change; if this occurs, older revisions of that form should no longer be used for data collection.
- If the form is revised without affecting the data collection - i.e., the wording of an item is revised - only the revision date of the form will be changed.

7.9. Missing data

- If a data item is missing and cannot be obtained when the form is completed or reviewed, write the appropriate code in the first left hand space of the empty data field:

  ? = data temporarily missing or inconsistent; to be collected or resolved in the near future; items keyed with a ? will need to be followed up on and resolved
  d = patient does not know the answer
  n = not applicable in this situation
  m = data missing
  r = patient refused

- When using any of the above codes, the entire data field does not need to be filled with the code (e.g., a missing height would be completed as m _ _ _._).

- If data are missing on the form, an explanation for the missing values should be written on the form and keyed to the database in the General Comments section of the keying.

- It is important to keep the number of missing data items at a minimum since resulting conclusions and paper publications depend on complete data, especially at the Baseline Visits.

- If an item is missing at the time the form is filled out, but is expected to be collected in the near future, record "?" rather than "M" code for the item on the form. The "m" code should only be recorded for data that are actually missing. The screening visit windows are broad enough to allow you to collect all data within the allotted time windows.

- If the data system will not accept a value, because it is out of range, please contact the DCC. In the meantime, record "?" rather than "m" on the form.

- If there is a valid reason that a required baseline laboratory value is missing, fax the LR or LS form to the DCC with the reason for the missing value.

- Participants cannot be enrolled until all "?"s keyed on the forms have been resolved.

7.10. Administrative sign off

- Each form contains a section for administrative sign off.
- These items include the Clinical Coordinator PIN and signature and the date the form was reviewed.
- Depending on the form, they may also include the PIN and signature of other staff.

It is the standard of practice with NIH funded studies to certify study physicians who assume responsibility for the accuracy and integrity of the sponsored studies. Coordinators are certified separately based on their professional qualifications and privileges even though the functions fulfilled may overlap functions of the study physician.

On the CyNCh data collection forms that require the Physician's signature, the signature is the assurance that as the clinical center's principal investigator, they are assuming responsibility for the accuracy of the data recorded on the study form. This does not require that the study physician completes the forms or performs the procedures, but does require assumption of responsibility signified by signing the CyNCh forms. This is also the standard of practice required by the FDA for case-report forms completion.

7.11. Handling forms

Form duplication

- The forms will be available on the NASH CRN website.
- You can print master copies from the website and then photocopy as needed or print as needed from the website – if you print copies ahead of time, do not print huge quantities as forms may be revised, especially in the early days of a study.
- The forms will also be available for printing from the data system.
- If a master copy gets frayed or faded, print a new master — always use clear copies for reproduction masters.

Form storage

- Forms for patients registered but not enrolled in CyNCh should be kept in a single folder in a locked room or locked filing cabinet.
- Each patient who is enrolled in CyNCh will have a patient file – either a notebook or file folder which is kept in a locked room or locked filing cabinet. The patient file should contain all CyNCh documents for the patient – consents, forms, appointment schedule, labels, and randomization materials. The forms should be arranged in the notebook or folder chronologically by visit. Tabs can be used to separate the visits.

7.12. Data rounding rules

To round data, examine the digits following the last position required on the form:

- If the first digit following the last data position required for the response is less than 5, leave the digit in the last data position required for the response unchanged, e.g., if you need to round to _._, then 4.73 rounds to 4.7 and 1.44 rounds to 1.4
- If the first digit following the last data position required for the response is 5 or more, round up the digit in the last data position required for the response, e.g., if you need to round to _._, then 4.78 rounds to 4.8 and 4.75 rounds to 4.8

When completing a calculation for CyNCh, apply the rounding rule only at the last step, when required to record a quantity on the CyNCh form.

7.13. Data audits and edits

Data audits

- The Data Coordinating Center will serve as the site monitor.
- The Data Coordinating Center will conduct periodic data audits as a quality control measure.
- Audits may be done by mail or on-site.
- During an audit, the forms will be reviewed to see if they were completed and keyed correctly; the forms will also be checked against the source documents to be sure that values were transcribed correctly.

Source documents include but are not limited to:

- Liver biopsy pathology reports
- MRI reports
- Laboratory test result reports
- Medical records for archival information
- Institutional drug accountability logs
- There are no source documents for questionnaires (the questionnaires are the original documents for the data collection)

Data edits

- Computerized data edits will be sent to the clinics periodically.
- The data edits check for consistency and questionable values in the database.

Changes resulting from audits or edits

- Changes made to the forms as a result of an audit or an edit should be marked "per audit" or "per edit" and should be dated and initialed.

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8. Quality assurance

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8.1. Site visits

Purpose

- Conduct an audit of selected patient data
- Review documentation and procedures for CyNCh
- Tour facilities
- Discuss with clinical center personnel any problems that have occurred or that are expected to occur in conducting the study

The following regulatory and study documents should be available or accessible:

- IRB communications organized with original approval letters, revision approvals, annual renewals, serious adverse event forms, and any communications regarding concerns or special requests from clinical center review board
- Signed and dated consent and assent forms for all participants including the date and signature of a witness
- Documents including CyNCh Protocol, PPMs, and SOPs
- Study forms for participants should be available for data audit

Participants

- At least two DCC personnel will attend the site visit. At least one person from another CyNCh clinical center will also attend. Representatives from other resource centers associated with the NASH CRN may also attend.
- NASH CRN certified staff from the clinical center

Reviewed during site visit

- IRB documentation
  - Original approval
  - Annual renewals (if applicable)
  - IRB submissions
  - Approval for updated consent and assent forms and protocol

- Documents
  - Directory
  - SOPs
  - Forms Book
  - PPMs
  - Protocol

- Enrollment and retention
  - Status
  - Recruitment and retention strategies
  - Problems
  - Losses to follow-up

- Personnel
  - Certification status
  - Personnel changes
  - Backup plans for personnel in event of absence

- Clinical management
  - Adverse event reporting procedures
  - Study procedures
  - Clinical center coordination
  - Study drug storage and dispensing
  - Scheduling
  - Clinical center concerns or problems

- Participant files
  - Security
  - Organization
  - Consent statements

- Specimen shipment
  - Comparison of specimens expected and received
  - Shipping procedures and problems
  - Shipping supplies

- Protocol performance
  - Protocol deviations

- Forms and data management
  - Monthly form status reports
  - Source documentation
  - Data audit (selected patients)
  - Eligibility criteria
  - Adverse events
  - Death reports

- Previous site visit report
  - Action items follow-up
  - Data audit follow-up

Site visit followup

- A list of action items is compiled at the end of the site visit to identify items which require further action. The procedure for site visit action item follow-up is:
  - Action items will be listed at the end of the site visit report.
  - Clinical centers will be required to respond to action items within 30 days of receipt of the site visit report. Responses should be in writing and sent to the DCC.
  - The DCC will be required to respond to the action items within 30 days of the completion of the site visit report. The DCC will send a written report to the clinical center.

8.2. Performance monitoring

- The DCC will generate enrollment reports that will provide a count of participants enrolled at each clinical center.

- On approximately a quarterly basis, the DCC will generate reports summarizing the performance of all clinical centers. These reports will include information on enrollment and the percentage of expected visits for which documentation has been entered into the CyNCh data system. Also, for those visits for which data have been entered, the report will show the percentage of missed visits, the completeness of data collection, the timeliness of data entry, and protocol deviations. Performance reports will be reviewed by the Steering Committee, and the Steering Committee will make decisions regarding actions to be taken in the event that a clinical center is performing poorly.

8.3. Data quality surveillance

General procedures

- Quality assurance of data accuracy will occur routinely through three main procedures: data entry checks, monthly checks for completeness and edits, and form audits.

- In addition, detection of problems may occur during data analysis. For example, in preparing reports for Steering Committee meetings, problems may be discovered. Outliers and unusual variations or patterns in the data are examined and may reveal problems.

- Quality assurance of data analysis is achieved by independent replication of key analyses within the DCC and review of reports by multiple individuals before distribution.

Data entry checks

- The data system will contain checks during the data entry process of range, logic, and consistency of items within forms.

- The data system will perform checks between forms to ensure that the same fields entered on different forms match.

- A double data entry system will be used for all forms.

Monthly check for completeness and edits

- On a monthly basis, after receipt of data transmittals from the clinical centers, the DCC will generate a database report of:
  - number of participants enrolled
  - missed visits
  - incomplete visits (missing or pending forms)
  - missed specimen collection or shipment
  - edits (see below)

- Edits are run on the database of the keyed forms monthly. Checks for missing, out-of-range, unusual and inconsistent values, cross-form checks and arithmetic errors are some of the types of checks performed. A listing of edits is sent to each clinical center for resolution. The clinical center must respond to each edit on the listing, make appropriate changes to the forms and database, compute documentation of each change, and file the documentation with the edited data collection form. Items that cannot be corrected (e.g., missing values, unusual measures) are entered into a database at the DCC. These items are excluded from future edits. A hard copy of the edits with each resolution should be kept in a notebook located at the clinical center.

Forms audits

On a periodic (approximately monthly) basis the DCC selects and requests copies of forms for specific participants be sent by each clinical center to the DCC for auditing.

- Audited forms are compared with the database; discrepancies are noted and queried.
- Audited paper forms are also inspected for other problems, which are noted and queried.
- Each clinical center will be required to resolve discrepancies from the audit report and fax the resolutions to the DCC within 5 days.
- The DCC will generate a summary report of the audit discrepancies by clinical center to be distributed to all CyNCh centers.
- Discrepancy rates over time by clinical center are reported to the Steering Committee.

NASH CRN

Nonalcoholic Steatohepatitis
Clinical Research Network

Cysteamine Bitartrate Delayed-Release for the Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in Children (CyNCH) Trial

Standard Operating Procedures
Part II: Administrative

29 February 2012

NASH CRN
CyNCH
Standard Operating Procedures - Part II:
Administrative

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CyNCH SOP II: Administrative

1. Organization

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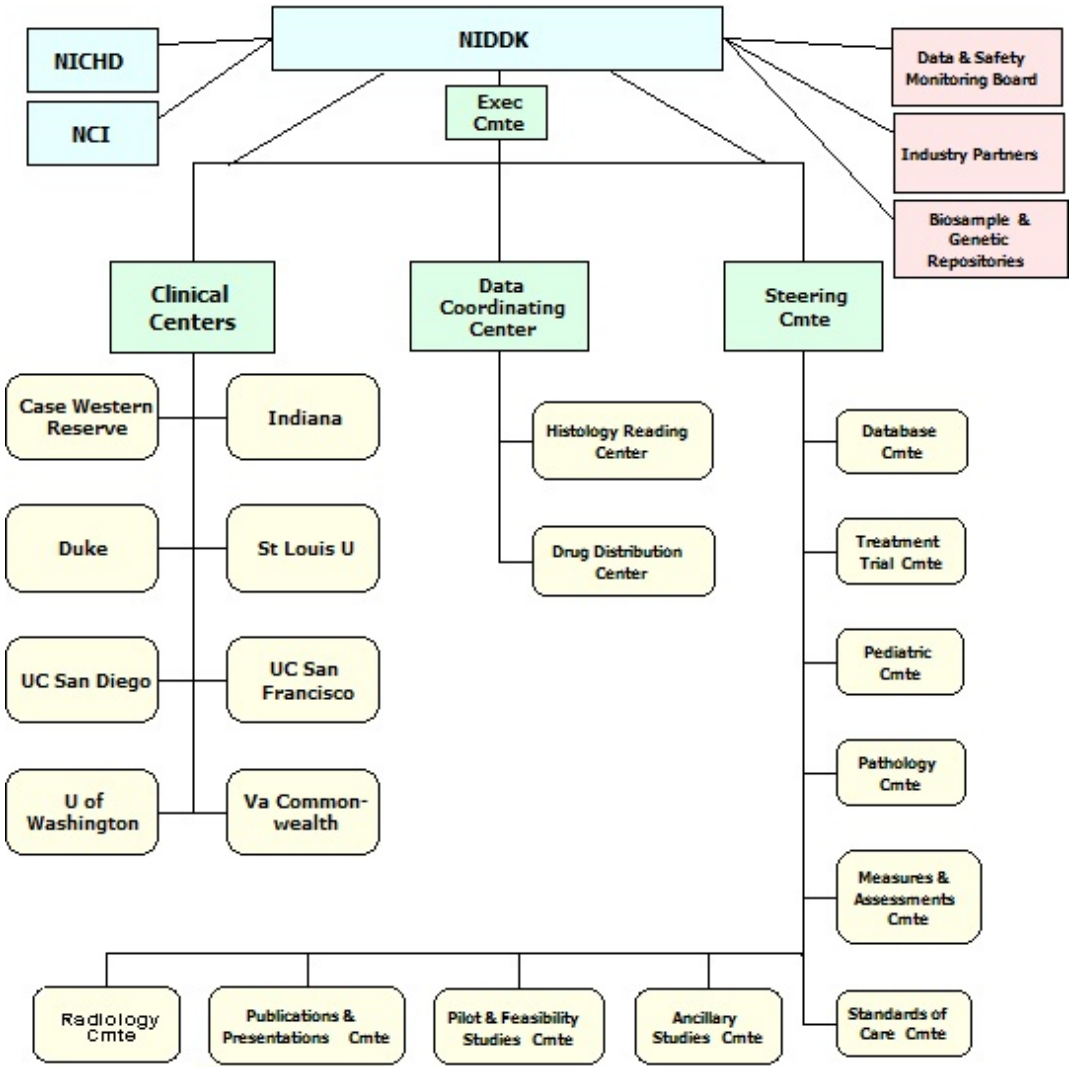
1.1. Overview


NIDDK
NICHD
NCI
Exec Cmte
Data & Safety Monitoring Board
Industry Partners
Biosample & Genetic Repositories
Clinical Centers
Data Coordinating Center
Steering Cmte
Case Western Reserve
Indiana
Duke
St Louis U
UC San Diego
UC San Francisco
U of Washington
Va Common-wealth
Histology Reading Center
Drug Distribution Center
Database Cmte
Treatment Trial Cmte
Pediatric Cmte
Pathology Cmte
Measures & Assessments Cmte
Standards of Care Cmte
Radiology Cmte
Publications & Presentations Cmte
Pilot & Feasibility Studies Cmte
Ancillary Studies Cmte

1.2. NIDDK Project Office personnel

Name	Role
Edward C. Doo, MD	Project Official
Averell Shaker, MD	Project Official
Jay H. Hoofnagle, MD	Advisor
Rebekah Van Raaphorst, MPH	Health Research Administrator
Rebecca Torrance, RN, MSN	Clinical Trials Specialist
Sharon Bourque	Grants Management Specialist

1.3. Study Co-chairs

Name	Institution
Arun J. Sanyal, MD	Virginia Commonwealth University
Joel Lavine, MD, PhD	Columbia University

1.4. Clinical Centers

Clinical Center	Principal Investigator
Case Western Reserve University (CWRU)	Arthur J. McCullough, MD
Cleveland Clinic Foundation (CCF)	
Cincinnati Children's Hospital (CINC)	Stavra Xanthakos, MD
Duke University Medical Center (DUKE)	Anna Mae Diehl, MD
Northwestern Children's Memorial Hospital (NWU)	Peter Whitington, MD
Johns Hopkins Children's Center (JHU)	Ann Scheimann, MD
Indiana University (IU)	Naga Chalasani, MD
Riley Hospital for Children	Jean Molleston, MD
Saint Louis University (SLU)	Brent A. Tetri, MD
Cardinal Glennon Children's Hospital	Ajay Jain, MD
Texas Children Hospital, Baylor University (BCM)	Stephanie Abrams, MD
Columbia University	Joel E. Lavine, MD, PhD
University of California, San Diego (UCSD)	Jeffrey Schwimmer, MD
	Rohit Loomba, MD
University of California, San Francisco (UCSF)	Norah Terrault, MD, MPH
	Philip Rosenthal, MD
California Pacific Medical Center (CPMC)	Raphael Merriman, MD
Virginia Mason Medical Center (VMMC)	Kris V. Kowdley, MD
Seattle Children's Hospital (UW)	Karen Murray, MD
Virginia Commonwealth University (VCU)	Arun J. Sanyal, MD
Mount Sinai Kravis Children's Hospital (MSCH)	Nanda Kerkas, MD

1.5. Data Coordinating Center personnel

Name	Role
James Tonascia, PhD	Director
Aynur Ünalp-Arida, MD, PhD	Deputy Director
Jeanne M. Clark, MD, MPH	Co-Investigator
Patricia Belt, BS	Project Coordinator
Mika Green, MA	"
Milana Isaacson, BS	"
Laura Miriel, BS	"
Alice Sternberg, ScM	"
Ivana Vaughn, MPH	"
Michele Donithan, MHS	Biostatistician
Kevin P. May, MS	"
Mark Van Natta, MHS	"
Laura Wilson, ScM	"
Kathie Yates, ScM	"
John Dodge	Forms Development
Jill Meinert	"

Note: The Data Coordinating Center is located in the Johns Hopkins University, Bloomberg School of Public Health, Department of Epidemiology

1.6. NICHD

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) has provided additional support for the pediatric component of the NASH CRN.

Project Officer
Gilman Grave, MD

1.7. NCI

Liver histology is the primary outcome in NASH CRN studies and David Kleiner, a pathologist from the National Cancer Institute, is the lead pathologist for the NASH CRN and co-chairs the NASH CRN Pathology Committee with Elizabeth Brunt (from Washington University in Saint Louis). The committee members consist of two co-chairs and seven additional pathologists, one from each of the other seven clinical centers participating in the NASH CRN.

Lead Pathologist
David Kleiner, MD, PhD

1.8. Resource Centers

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1.8.1. NIDDK Biosample Repository

NIDDK has contracted with Fisher BioServices to serve as a Biosample Repository for NIDDK sponsored studies, including the NASH CRN. Serum, plasma, and snap frozen liver tissue will be banked at the NIDDK Biosample Repository at Fisher BioServices for all NASH CRN studies (main studies, substudies, ancillary studies, or other). Shipping materials for sample shipment will be provided by the NIDDK Biosample Repository at Fisher BioServices. Specimens that have not been used by the study's end will become available to other researchers, under the supervision of the NIDDK.

Principal Investigator
Heather Higgins

1.8.2. NIDDK Genetics Repository

NIDDK has contracted with a facility at Rutgers University to serve as a Genetics Repository for NIDDK sponsored studies, including the NASH CRN. DNA will be banked for future genetics studies (NASH CRN substudies, ancillary studies, or other). DNA that have not been used by the study's end and for which study participants gave consent will become available to other researchers, under the supervision of the NIDDK.

Principal Investigator
Douglas Fugman, PhD

Assistant Managing Director
David A Toke, PhD

Contact person
Dana Garbolino

1.8.3. Histology Review Center

Purpose

- To act as the central pathology reading center for confirmation and/or adjudication of NAFLD, NASH, and NASH related cirrrhosis
- To act as the NASH CRN liver tissue repository for slides and surgical pathology reports
- To act as a liver tissue slide resource for main studies, substudies, and ancillary studies
- To maintain a database with complete inventory of banked liver tissue biopsy specimens

Slide shipment and histology review center contact information

- The slide preparation and shipping process is described in the FLINT SOP IV = Liver Biopsy and NAFLD Histology Scoring System: Clinical Center Operations. Slides shipped to the histology review center should be shipped to the address below:

  Histology Review Coordinator (Pat Belt)
  NASH CRN Data Coordinating Center
  615 N. Wolfe Street, Room W5010
  Baltimore, MD 21205
  Telephone: (410) 955-8175
  Fax: (410) 955-0932

Histology Review Center staff

- Histology Review Coordinator
- NASH CRN DCC backup staff
- NASH CRN support for computer maintenance

NASH CRN clinical center pathologists

- Cynthia Behling - UCSD
- Elizabeth Brunt (co-chair) - SLU
- Melissa Contos - VCU
- Oscar Cummings - IU
- Linda Ferrell - UCSF
- Cynthia Guy - DUKE
- David Kleiner (co-chair) - NCI
- Rish Pai, CWRU
- Michael Torbenson - JHU
- Matthew Yeh - UW

1.8.3. Histology review center

Schedule for central histology review

- Four times a year for 2 days, or more frequently as needed

Equipment

- Olympus model BX51 ten-headed research microscope
- 10-head microscope table and Harter chairs with gas lift
- Rear projection unit
- Olympus Q-color3 Color Digital Camera (3 megapixels)
- Microscope maintenance contract
- Fisher Scientific stackable slide cabinets
- Secure storage facility
- Dedicated Dell Optiplex Desktop computer, model GX270
- 20 inch flat panel digital monitor

1.9. Committees

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1.9.1. Steering Committee

- Major decision making body for NASH CRN
- Provides oversight in planning and conduct of study
- Votes on all important decisions and approves the final database and protocol and any amendments or modifications of the protocol
- Consists of principal investigators of each of the adult and pediatric clinical centers, the principal investigator of the Data Coordinating Center, and the NIDDK project scientist
- Each member has one vote in any decision requiring formal vote
- Ex officio nonvoting members include NIDDK scientific staff

1.9.2. Executive Committee

- Manages day-to-day major issues of NASH CRN, making decisions in periods between Steering Committee meetings
- Organizes and sets agenda for Steering Committee meetings
- Provides oversight of study
- Consists of NASH CRN co-chairs, principal investigator of Data Coordinating Center, NIDDK project scientist, and NIDDK scientific expert(s)

1.9.3. Subcommittees of the Steering Committee

Database 2 Protocol Committee

- Prepares the final written protocol for the study and thus prepares summary, background information, study design, inclusion and exclusion criteria, monitoring schedule, adverse event reporting, statistical analysis, patient protection, and references section of the protocol for the NAFLD Database 2 study
- A subcommittee of the Database 2 Committee prepares the master consent form for the study
- The details of the NAFLD Database 2 design are developed by the Database 2 Committee, but major decisions in the design and the final protocol are approved by the Steering Committee
- Consists of a chair and at least three other principal investigators or co-principal investigators from the clinical centers as well as all members of the Executive Committee

Members:

Norah Terrault (chair - adult), UCSF
Joel Lavine (chair - pediatric), CU
Stephanie Abrams, SLU
Elizabeth Brunt, SLU
Anna Mae Diehl, DUKE
David Kleiner, NCI
Jean Molleston, IU
Phillip Rosenthal, UCSF
Arun Sanyal, VCU
Claude Sirlin, UCSD
Brent Tetri, SLU
Peter Whitington, DUKE

Pathology Committee

- Develops the pathological criteria for diagnosis, staging, and grading of the liver biopsies
- Develops a system for grading the severity of NASH and staging the degree of fibrosis
- Makes recommendations regarding the reading of biopsies and prepare studies of the intra- and inter-observer study variation in readings of biopsies
- Helps in the analysis of data as they relate to histological features
- Consists of the lead pathologist from each of the clinical centers, up to two pathologists assigned by NIDDK, a statistical advisor from the Data Coordinating Center, and an NIDDK staff member.

Members:

Elizabeth Brunt, (co-chair) SLU
David Kleiner, (co-chair) NCI
Cynthia Behling, UCSD
Melissa Contos, VCU
Oscar Cummings, IU
Linda Farrell, UCSF
Cynthia Guy, DUKE
Arthur McCullough, CWRU
Rish Pai, CWRU
Arun Sanyal, VCU
Michael Torbenson, JHU
Matthew Yeh, UW

Standard of Care Committee

- Develops policies about the current recommended standard of care of NAFLD and NASH.
- Makes recommendations regarding diet, exercise, weight loss, avoidance of unnecessary medications and alcohol use.
- Develops a rigorous set of detailed instructions for patients that can be translated into appropriate patient oriented materials.
- Insures that all patients receive optimal medical recommendations regarding management of NAFLD and NASH.
- Consists of a chair and at least three principal investigators or co-principal investigators from the clinical centers, two designated members from the Data Coordinating Center and an NIDDK staff member.

Members:

Rohit Loomba (chair), UCSD
Stephanie Abrams, SLU/BCM
Jean Molleston, IU
Arun Sanyal, VCU
Raj Vappahanchi, IU

Pediatric Committee

- Develops the NAFLD Database 2 Pediatric protocol and recommendations regarding standard of care of NASH for pediatric aged patients.
- Defines the lower age of enrollment in the study and will delineate all of the variations from the standard protocol database, consent forms, questionnaires, and recommendations for standard of care that are applicable to children.
- Recommends on frequency of standard of Cave liver biopsy in children.
- Consists of a chair and at least three principal investigators from the clinical centers, two designated members from the Data Coordinating Center and an NIDDK staff member.

1.9.3. Subcommittees of the steering committee

Members:

Joel Lavine (chair), UCSD
Stephanie Abrams, SLU/BCM
Ajay Jain, SLU
Jean Molleston, IU
Karen Murray, UW
Ann Sheimann, DUKE/JHU
Jeffrey Schwimmer, UCSD
Peter Whitington, DUKE/NWU
Stavra Xanthakos, CWRU/CINC

Ancillary Studies Committee

- Develops the policy for review and approval of ancillary studies of the NASH CRN.
- Reviews applications for ancillary studies of the NASH CRN and makes recommendations for approval or disapproval to the Steering Committee.
- Communicates the decision of the Steering Committee to the proposing investigators and the ancillary study liaison.
- Maintains a list of all proposed ancillary studies indicating approval status and the liaison. For approved studies, the list will indicate initiation date and the NASH CRN centers participating in the ancillary study.
- Maintains a list of allocations of existing NASH CRN samples by ancillary studies.

Members:

Arthur McCullough (co-chair), CWRU
Peter Whitington (co-chair), DUKE/NWU
Elizabeth Brunt, SLU/WU
Naga Chalasani, IU
Anna Mae Diehl, DUKE
Ed Doo, NIDDK
David Kleiner, NCI
Kris Kowdley, VMMC
Arun Sanyal, VCU
Jeffrey Schwimmer, UCSD
Brent Tetri, SLU
Norah Terrault, UCSF
James Tonascia, JHU-DCC

Presentations and Publications Committee

- Develops the policy for publications in regards to proposal of manuscripts, reviews and approval of manuscript proposals, assignment of tasks in analysis and writing, and other issues related to publications.

- Develops the policy for presentations in regards to proposal of presentations, review and approval of presentation proposals, assignment of tasks in analysis and writing, review of presentations, authorship policy, and other issues related to presentations.
- Makes recommendations to the Steering Committee about topics for publications.
- Makes recommendations to the Steering Committee about topics for presentations at national and international meetings.
- Makes recommendations concerning the priority of manuscripts and presentations.
- Reviews proposals for publications and presentations and makes recommendations for approval or disapproval to the Steering Committee.
- Reviews manuscripts prior to journal submission and reviews presentations prior to presentation.
- Mediates and settles all disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations. Investigators who preceive inequities in authorship or other problems relating to authorship should discuss these concerns with the P&P Committee chair; if the difficulty cannot be settled in this informal manner, the concerned investigator should submit a letter to the P&P Committee chair outlining the problem. The document will be reviewed and discussed by the P&P Committee, and a written reply will be made to the investigator. If P&P Committee deliberations fail to resolve such a dispute, the dispute will be submitted for resolution to the full SC, excepting those with a conflict of interest.
- Prepares and maintains a list of concepts for publications and prepare and maintain a list of approved NASH CRN publications, which shows the status of each manuscript from initiation through publication
- Consists of a chair elected by the SC and three clinical center principal investigators, an investigator from the Data Coordinating Center, and an NIDDK representative. The chair serves a one year term and three clinical center principal investigators serve for two-year terms. The members from the Data Coordinating Center and NIDDK serve for the duration of the NASH CRN.

Members:

Brent Tetri (co-chair), SLU
Philip Rosenthal (co-chair), UCSF
Elizabeth Brunt, SLU
Anna Mae Diehl, DUKE
Ed Doo, NIDDK
David Kleiner, NCI
Kris Kowdley VMMC
Joe Lavine, CU
Art McCullough, CWRU
Arun Sanyal, VCU
James Tonascia, JHU-DCC
Aynur Ünalp-Arida, JHU-DCC

1.9.3. Subcommittees of the steering committee

Radiology Committee

- Develop standardized imaging procedures for NASH CRN research protocols
- Provide oversight, technical support, and quality assurance for imaging procedures
- Provide a mechanism for central archival and analysis of images along with the DCC
- Make recommendations regarding new imaging technology related to NAFLD
- Propose new ancillary imaging studies
- Assist with the analysis of data and review of manuscripts and ancillary study proposals as relates to imaging features
- Consists of a radiologist from each NASH CRN Center that participates in imaging procedures, a Steering Committee member, a statistical advisor from the Data Coordinating Center, and an NIDDK staff member

Members:

Claude Sirlin (chair), UCSD
Mark Bydder, UCSD
Laura Carucci, VCU
Ed Doo, NIDDK
Kathryn Fowler, SW
Gavin Hamilton, UCSD
Kenneth Kraft, VCU
Joel Lavine, CU
Elmar Merke, Duke
Michael Middleton, UCSD
Aliya Qayyam, UCSF
Kumar Sandrasegaran, IV
Arun Sanyal, VCU
James Tonascia, JHU-DCC

1.10. Data and Safety Monitoring Board

Responsibilities

- To review the research protocols, informed consent documents, and plans for data and safety monitoring, including all proposed revisions
- To evaluate the progress of studies, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the clinical sites, and other factors that can affect study outcome
- To protect the safety of the study participants
- To report on the safety of the study participants and progress of the trial
- To consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
- To make recommendations to the NIDDK, the Steering Committee, and, if required, to the FDA and IRBs concerning continuation, termination, or other modifications of the studies based on the observed beneficial or adverse effects
- If appropriate, to review interim analyses of efficacy in accordance with outcomes and stopping guidelines, which are clearly defined in advance of data analysis
- To ensure the confidentiality of the study data and results produced for the purposes of interim study monitoring
- To assist the NIDDK by commenting on any problems with study conduct, enrollment, sample size and/or data collection

Membership

- Timothy Morgan, MD (Chair); VA Medical Center, Long Beach, CA
- Maureen M. Jonas, MD; Boston Children's Hospital
- David Reboussin, PhD; Wake Forest School of Medicine
- Richard Schreiber; Child and Family Research Institute
- Natalie Torok, MD; University of California, Davis
- Ruth Weinstock, MD, PhD; State University of New York

2. Policies

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2.1. Duality of interest disclosure

Policy

- Disclosure of financial relationships with companies or other entities that have interests in NASH research or NASH CRN activities

Purpose

- To avoid potential bias and susceptibility to influence from pharmaceutical, biotechnology, and medical device manufacturers or other entities whose products or services will be used or tested in the NASH CRN, or whose products or services would be directly and predictably affected in a major way by the results of NASH CRN studies
- To avoid the appearance of bias or susceptibility

Disclosure procedure

- Statement of relationships with pharmaceutical and medical device manufacturers or other entities whose products or services are used, tested, or affected by the NASH CRN will be completed
- In general, relationships with a combined level of interest to the investigator, spouse, and dependent children must be disclosed in the following categories:
    - No interest
    - $10,000 or less or 5% equity or less
    - More than $10,000 or more than 5% equity
- Initial duality of interest disclosure statements are to be updated annually
- Statement format to be drafted and adopted by the Steering Committee
- Statements will be collected by the DCC or other body appointed by the Steering Committee

Review procedure

- Statements will be summarized by the DCC
- Summaries of collected statements will be reviewed by NIDDK and by the Steering Committee and will be included in Steering Committee meeting books
- Statements will be kept on file at the DCC or other location selected by the Steering Committee

Who must sign a duality of interest disclosure statement

- Principal investigators
- Co-principal investigators
- Investigators who enroll study patients
- Voting members of the Steering Committee
- DSMB members
- Members of standing committees
- Advisors or consultants for the NASH CRN

2.1. Duality of interest disclosure

Examples of interests that must be disclosed

- Ownership of stock, equity, or other financial interest in any company or entity involved with a NASH CRN study (details of the relationship need not be disclosed)
- Employment, office, or directorship in any company or entity involved with the NASH CRN
- Personal compensation from any company or entity involved with the NASH CRN
- Consulting or advisory arrangements with any company or entity involved with the NASH CRN
- Grants, contracts, research, training, or other support from any company or entity involved with the NASH CRN
- Travel grants to educational symposia provided by any company or entity involved with the NASH CRN
- Intellectual property rights related to the activities of the NASH CRN
- Other relationships in which there is or seems to be a dependency relationship between a NASH CRN investigator and an entity or company involved in the NASH CRN
- Relationship with a company or other entity that may affect academic advancement or status, such as sponsorship of an endowed chair or establishment of a fund for use by the NASH CRN investigator

Study duration to which policy applies

- For the duration of NASH CRN funding or activity, and beyond that, for up to two years or until all major publications are completed

Possible consequences of a relationship judged to be a conflict of interest with the NASH CRN

- No action; disclosure alone is sufficient
- Relationship is described in a footnote to a paper
- Investigator is banned from authorship of one or more papers (depends on relationship of conflict to content of paper)
- Investigator may not vote on any issue related to a company or other entity with which they have a relationship, regardless of the monetary value or nature of the relationship; however, voting rights on such issues may be delegated to a co-investigator, as long as the co-investigator has no relationship with the company or entity

2.2. Presentations and Publications Committee

1. Charge of the Presentations and Publications Committee

The purpose of the Presentations and Publications (P&P) Committee is to oversee and provide guidance relative to reporting study data and to assure that study reports have expert input, a high standard of scientific quality, responsible conclusions, sound interpretations, and fulfill the overall objectives of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). The charge of the P&P Committee is to:

- Develop and maintain the policy for publications in regards to proposal of manuscripts, review and approval of manuscript proposals, assignment of tasks in analysis and writing, review of manuscripts, authorship policy, and other issues related to publications
- Develop the policy for presentations in regards to proposal of presentations, review and approval or presentation proposals, assignment of tasks in analysis and writing, review of presentations, authorship policy, and other issues related to presentations
- Make recommendations to the Steering Committee about topics for publications
- Make recommendations to the Steering Committee about topics for presentations at national and international meetings
- Make recommendations concerning the priority and sequential order of submission of manuscripts and presentations
- Review investigator-initiated proposals for publications and presentations and make recommendations for approval or disapproval to the Steering Committee based on factors such as anticipated value to the scientific community, overlap with other papers, and appropriateness of the proposed writing committee
- Review manuscripts and recommend changes to the writing committee and then review revised manuscripts before submission to the NIDDK for comment
- Review manuscripts prior to journal submission and review abstracts and presentations prior to presentation
- Mediate and settle all disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations. Investigators who perceive inequities in authorship or other problems relating to authorship should discuss these concerns with the P&P Committee chairperson; if the difficulty cannot be settled in this informal manner, the concerned investigator should submit a letter to the P&P Committee chairperson outlining the problem. The document will be reviewed and discussed by the P&P Committee, and a written reply will be made to the investigator. If P&P Committee deliberations fail to resolve such a dispute, the dispute will be submitted for resolution to the full Steering Committee, excepting those with a conflict of interest

- Prepare and maintain a list of concepts for publications and prepare and maintain a list of approved NASH CRN publications, which shows the status of each manuscript from initiation through publication

The purview of the P&P Committee includes publications and presentations arising from NASH CRN main studies, substudies, pilot and feasibility studies, and ancillary studies.

2. Goals

- To promote timely, scientifically accurate, and high-quality presentation and publication of findings from NASH CRN studies
- To support broad and equitable participation by NASH CRN investigators in presentations and publications
- To define a set of equitable policies and procedures to determine authorship and the order in which authors are listed
- To review and select topics for publications and presentations, assign authors to writing groups, set priorities for publications and presentations, and monitor progress of publications and presentations
- To provide editorial support and timely review for presentations and publications
- To defend the academic freedom of NASH CRN investigators collectively to publish results emanating from the NASH CRN studies
- Impose limitations if needed on publication of results from any center(s) that could threaten the integrity of collective data

3. Scope

- These policies and procedures apply to original manuscripts (including methodology, validation, laboratory approaches), abstracts, oral and poster presentations, letters to the editor, meeting proceedings, and extended abstracts that include data collected as part of the NASH CRN. The policy and procedures also apply to review articles that include original NASH CRN data not previously published
- These policy and procedures apply to publications and presentations arising from NASH CRN main studies, substudies, pilot and feasibility studies, and ancillary studies
- The P&P Committee will propose amendments to the presentation and publication policy and procedures to the Steering Committee as necessary to clarify their intent

4. Presentations and Publications Committee membership

- The P&P committee consists of two co-chairs (one from an adult center and one from a pediatric center), 5 clinical center principal investigators, two representatives from the Pathology Committee, two investigators from the Data Coordinating Center, and an NIDDK representative. Chairs and members are either appointed by the NIDDK and approved by the Steering Committee or elected by the Steering Committee
- The chairperson serve until new chairs are recommended by the NIDDK or the Steering Committee
- The members from the Data Coordinating Center and NIDDK serve for the duration of the NASH CRN
- The number of consecutive or interrupted terms that a chairperson or other elected member may serve will not be limited
- Each member has one vote, except the two pathologists, who share one vote
- If a member is an author on a presentation or manuscript or otherwise has a conflict of interest, the member will recuse himself/herself from voting on the proposal, manuscript, or presentation

5. Types of publications

- **Main reports** arise from main studies and address the main objectives of main studies or report primary outcome data or design and methods of main studies. Examples of main reports are those that address the efficacy in the adult and pediatric treatment trials, and design and methods of NASH CRN studies
- **Secondary reports** arise from main studies and address secondary objectives of main studies or report data or design issues or methods that are more peripheral to the main studies than those addressed in main reports
- **Substudy reports** arise from substudy of the NASH CRN
- **Ancillary study reports** arise from an ancillary study of the NASH CRN
- **Pilot and feasibility reports** arise from a pilot or feasibility study of the NASH CRN
- Abstracts, meeting proceedings, extended abstracts, oral and poster presentations
- Letters to the editor

6. Writing groups and authorship issues

6.1 Writing groups

- Writing groups: The writing of manuscripts will be assigned to a writing group consisting of NASH CRN investigators, one of whom will be designated the Chair. The P&P Committee will nominate the writing group chair and members and send the selection to the Steering Committee for final approval. Investigators proposing manuscripts may suggest writing group membership to the P&P. An investigator proposing a manuscript is not assured lead authorship on that manuscript
- Investigators proposed to be writing group members must agree to participate in the writing group and must receive all drafts and comments as manuscripts are developed

6.2 Authorship criteria

- Authors should participate in the writing of the paper according to guidelines of the International Committee of Medical Journal Editors (see http://www.icmje.org/urm_main.html assessed on 25 November 2009, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (Updated October 2008) Publication Ethics: Sponsorship. Authorship, and Accountability")
- Those who participated in conception and design, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript relating to important intellectual content, and final approval of the manuscript should be included as authors. Expertise (eg, statistical, virology, or pathology) that relates directly to the conduct of the study is additional criterion for authorship
- Provision of study material or patients; data collection and assembly; administrative, technical, or logistic support; and obtaining funding do not necessarily merit authorship but should be considered on a case-by-case basis, especially when other contributions are included
- Honorary authorship will not be considered

6.3 Authorship format by type of report

- Main reports will have modified corporate authorship "The NASH Clinical Research Network". An appendix listing all investigators in the NASH CRN will be included, and the writing group will be designated in a footnote to the title page. The writing group will include limited number of investigators from clinical center, DCC, and NIDDK
- Secondary or lesser reports of main NASH CRN studies will have modified conventional authorship (Name1, name2, ..., and the NASH Clinical Research Network) or conventional authorship. An appendix listing all investigators in the NASH CRN will be included, journal permitting

- Substudy reports will have modified conventional authorship (Name1, name2, ... and the NASH Clinical Research Network) or conventional authorship. An appendix listing all investigators in the NASH CRN will be included, journal permitting
- Pilot and feasibility study reports will have modified conventional authorship (Name1, name2, ..., and the NASH Clinical Research Network) or conventional authorship. An appendix listing all investigators in the NASH CRN will be included, journal permitting
- Ancillary study reports will likely have conventional authorship. The NASH CRN does not control authorship of ancillary study papers. Ancillary study reports should acknowledge the role of the SC member who serves as the liaison for the ancillary study but the liaison does not necessarily need to be included as an author unless the SC member has materially participated in the ancillary study and meets the standard criteria for authorship. Ancillary study reports should also include in the acknowledgements the NIDDK grant number for any sites involved in the study and the DCC, if the DCC assisted with the study

6.4 General issues for naming authors

The following points apply when conventional or modified conventional authorship is used for a publication or presentation.

- Members of the writing group who fulfill criteria for authorship, plus any ad hoc contributors who fulfill criteria for authorship, will be listed as authors
- Order of authorship: The Chairperson of the writing group will propose the first author and authorship order to the P&P Committee based on the level of input into the manuscript The P&P Committee may amend the order of authorship to recognize an exceptional contribution to the study or the manuscript by an individual. Upon P&P Committee approval, the order will be submitted to the Steering Committee for final approval. For all manuscripts, factors to be included in decisions about order of authorship are contribution to concept, design, and analysis; role in drafting the article or revising it critically for important intellectual content; completeness and integrity of the data and specimens from the investigator's site; and leadership role
- For journals that limit the number of masthead authors, the following order of authorship will apply until the journal's limit is reached:
  – The writing group member who fulfill criteria for authorship
  – Other investigators identified by the writing group as having made special contributions to the concept, design, or analysis of the study
  – Other investigators identified by the writing group as having contributed special effort to the execution of the study
  – If the journal's limit of authors is reached before all writing group members who fulfill criteria for authorship are listed, all others in the writing group will be listed in an Acknowledgments section of the manuscript

7. Proposal of topics and review of proposed topics

- The DCC will maintain a continuously updated list of proposed and approved manuscripts and their status. This list is available on the password protected NASH CRN publication proposals web page.
- Any member of the NASH CRN may propose a manuscript. Non Steering Committee members should channel their requests through the Steering Committee member of their site who will forward the topic to the P&P Committee. Proposals must be submitted in writing to the P&P Committee by completion of the Abstract/Publication Proposal (PP) form which is available on the NASH CRN website (www.nashcrn.com, click on Publications). This form requires:
  – a brief description of the background, hypothesis, and purpose of the topic
  – a summary of the analysis plans
  – a description of the subjects to be included
  – a list of variables of interest
  – proposed writing group membership (including statistician) and proposed chair
  – for abstracts, the date of submission and date of the meeting
  – for manuscripts, target journals or book
  – sign-off by proposing investigator that he/she has reviewed the existing NASH CRN proposals and that the proposal does not significantly overlap with any existing proposals
- The DCC will distribute a copy of the proposals to members of the P&P Committee with a deadline for return of comments (or will schedule a conference call). P&P Committee members may propose additional or alternate writing group members. The P&P Committee will select the final writing group membership and appoint the writing group chair. The selection of writing groups and their Chairpersons will be submitted to the Steering Committee for final approval
- Criteria for judging proposals:
  – scientific merit of the hypothesis or aim of the proposal
  – availability of appropriate data to address the hypothesis or aim
- If overlap in content exists between or among proposals, the P&P Committee will either eliminate overlap or consolidate the proposals

8. Responsibilities of the writing group

- The chair of the writing group will be responsible for assigning tasks to other members of the writing group and for overseeing the completion of these tasks on schedule
- Manuscripts will be prepared at the center of the writing group Chair
- All data analysis will be done through the DCC (mainline papers) or appropriate statistician at a NASH CRN site
- When the manuscript is judged ready for internal review, the chair will submit the completed manuscript to the DCC for distribution to the P&P Committee members. If a writing group does not complete its work or fails to meet timeline milestones, the P&P Committee may reassign the roles of chair or select new writing group members. This exigency may be exercised if no draft is produced within 3 months of the availability of a clean data set

- If, during the course of work on a manuscript, the analysis is found to be too broad for a single manuscript, the writing group may suggest to the P&P Committee that the data would be more suitable for more than a single manuscript. The writing group must notify the P&P Committee that they plan to narrow the scope of the manuscript
- Writing group members may withdraw or be withdrawn from the writing group if their participation is insufficient to warrant co-authorship

9. Acknowledgments to be included in publications and presentations

- All NASH CRN manuscripts must include an acknowledgment of NIDDK funding, with specific grant numbers, as well as NIH funding numbers of participating General Clinical Research Centers. A NASH CRN support statement can be found on the NASH CRN website (www.nashcrn.com, click on Publications). Acknowledgment of CRADA partners should be included as well. When appropriate, other institute or center support is to be acknowledged (e.g., National Institute of Child Health and Human Development, National Cancer Institute). Grant numbers do not have to be specified on acknowledgments for abstracts and presentations
- Ancillary study manuscripts should include an acknowledgment of the Steering Committee member who served as the ancillary study liaison and the grant number for the clinical center associated with the ancillary study

10. Review of manuscripts

- The P&P Committee will serve as the editorial review committee for all manuscripts
- Manuscripts that are judged ready for P&P review should be submitted to the DCC for distribution to the P&P Committee members
- Two primary reviewers with relevant expertise will be identified by the P&P Committee and DCC from within the NASH CRN membership to provide a timely review (within two weeks) of the manuscript for editorial clarity and data integrity (ancillary study reports are excluded)
- The DCC will simultaneously do their own review of the analysis and statements about the NASH CRN protocol
- The DCC will also send all manuscripts received for P&P review to the Steering Committee members for voluntary comments to the P&P Committee. A deadline for all comments will be specified
- The results of the assigned, voluntary, and DCC reviews will be collated by the DCC and sent to the writing group chair for preparation of a revised manuscript. The writing group chair may discuss the planned response of the writing committee to the comments with the P&P Committee chair or full committee by conference call if needed
- A revised manuscript will be reviewed by the P&P Committee for appropriate responsiveness to the comments. If the response is acceptable, the revised manuscript will be forwarded to the NIDDK for comments

- Under certain circumstances, the formal review by the NIDDK can be requested by the writing committee to occur concurrently with the internal P&P and DCC reviews. This option would be considered when the writing committee feels that there is significant time pressure to accelerate the review process because of competitive work by others or to take advantage of funding opportunities
- All papers arising from the NASH CRN, including ancillary study reports, must be reviewed by NIDDK prior to journal submission. The writing group chair will submit the manuscript to the DCC for distribution to the NIDDK project officer and other relevant NIDDK staff after receiving approval from the P&P to do so
- Disagreements between the NASH CRN Steering Committee and the NIDDK staff on the merits of journal submission of a specific manuscript will be mediated through discussion on Steering Committee conference calls, ad hoc conference calls and during face to face Steering Committee meetings
- The NIDDK project officer will notify the DCC when the manuscript is approved for journal submission
- If a dispute occurs between the authors and the P&P Committee, resolution of the dispute is the responsibility of the Steering Committee
- Although approval by CRADA/CTA partners is not required, as a courtesy, manuscripts that relate to work carried out through the support of a CRADA/CTA will be submitted to the relevant CRADA/CTA partner at the same time as submission to the P&P. CRADA/CTA partners will not have authority to prevent or delay publication. CRADA/CTA partners will be given deadline for return of comments
- Ancillary study reports will be sent to one NASH CRN member with relevant expertise for review for accuracy of statements about the NASH CRN resources used in the ancillary study and for appropriate acknowledgment of NASH CRN. The role of the NASH CRN in ancillary studies is further outlined in the NASH CRN Ancillary Studies Policy

11. Publications priorities

- No investigator may jeopardize the publication of NASH CRN study results in a peer-reviewed journal by releasing or presenting data prematurely. Local press releases are to be timed to coincide with publication of manuscripts and must respect any applicable publication embargoes
- No individual site will be permitted to publish site-specific NASH CRN results without the approval of the Steering Committee

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12. Presentations, abstracts, and letters to the editor

- Presentations of NASH CRN data at national and international meetings must be approved. The approval process may entail review of slides and printed material by the same mechanism as that used to review abstracts. P&P Committee approval is not required for local presentations and accompanying syllabus material (eg, medical school lectures, continuing education courses, grand rounds lectures, research seminars, etc). Investigators are encouraged to consult the Committee chairperson when questions about the propriety

of a local presentation arise. If the chair cannot address such questions readily, the issue will be considered by the entire P&P Committee (via conference call or written communication)

- Presentations and abstracts will generally use modified conventional authorship (name 1, name 2, ..., etc, and the NASH Clinical Research Network) and will include acknowledgment of NIDDK funding
- The DCC will be responsible for data analysis and final slide preparation for NASH CRN corporate presentations
- Investigator-initiated abstracts that require data analysis assistance from the DCC must be proposed to the P&P Committee at least 3 months prior to the internal review submission deadline (use the same form used to propose a manuscript). The P&P Committee will review the proposal, and if approved will prioritize the analysis requests, in consultation with the DCC
- Completed abstracts are to be submitted to the P&P Committee at least 6 weeks prior to submission to the organization sponsoring the meeting. The abstract will be circulated to the full P&P Committee with a ballot for approval as written, approval with revisions, disapproval, or tabled for further discussion by the Steering Committee. A majority of the P&P Committee members responding must approve the abstract for it to be approved for submission. Abstracts submitted fewer than 6 weeks prior to the due date will be reviewed in time for submission if possible, but the P&P Committee cannot guarantee to complete the review in time to meet the due date
- Letters to the editor are to be approved according to the same process as that used for abstracts

13. Reprints and postings to the NASH CRN website

- Reprints of mainline manuscripts authored by "The NASH Clinical Research Network" will be purchased by the DCC, and requests for reprints may be addressed to the DCC. Reprints for all other manuscripts are the responsibility of the writing group chair (who may determine that purchase of reprints is not feasible)
- Final versions of NASH CRN manuscripts will be posted on the NASH CRN website. Slide material prepared for presentation at national or international meetings will also be posted on the NASH CRN website

Acknowledgments:

In drafting the NASH CRN Presentations and Publications Policy and Procedures, we referred to the following sources: Publication and Presentation guidelines of the Virahep-C and HALT-C studies sponsored by the NIDDK, and the Presentation and Publication Policy and Procedures of the National Emphysema Treatment Trial sponsored by the NHLBI.

2.3. Ancillary Studies Committee

1. Background and access to NASH CRN specimens

The NASH CRN studies comprise a large and well characterized population sample of individuals with various stages of nonalcoholic fatty liver disease, including steatosis, steatohepatitis, and NASH-related cirrhosis. To make the best possible use of this extraordinary resource, the NASH CRN encourages external investigators, as well as NASH CRN investigators, to develop ancillary studies.

Access by ancillary studies to NASH CRN specimens and data collected on participants will be governed by the NASH CRN Steering Committee and administered by the Data Coordinating Center. It is likely that access to baseline specimens and data from a NASH CRN study will be permitted to an ancillary study prior to the conclusion of the NASH CRN study, but only after the NASH CRN has determined that the baseline data are of a quality suitable for sharing. Follow-up specimens, data, and information about treatment assignment in a NASH CRN clinical trial are unlikely to be available until after the NASH CRN trial has ended, regardless of the timing of the ancillary study. Ancillary study investigators should be aware that there may be delays of possibly years before NASH CRN data are released.

NASH CRN datasets use the NASH CRN Patient ID number to link patient records. Ancillary study investigators should request data on the NASH CRN participants in their study by providing the NASH CRN ID numbers of the patients whose data are requested. The DCC will accept SAS, Excel, Access, ASCII, and other data files of records of NASH CRN ID numbers (word processing files are not acceptable, other identifiers are not acceptable).

Data and samples collected using NASH CRN central resources are governed by the NASH CRN Steering Committee; these are NASH CRN data and NASH CRN samples. The NASH CRN specimens and clinical data are provided to the ancillary study investigator with the understanding that all biomarker and genomic data generated through the ancillary study will be shared by the NASH CRN. Other measurements made on NASH CRN samples under an approved ancillary study protocol and paid for by ancillary study resources may be retained for the sole use of the investigator in publishing. However, the NASH CRN must be granted access to all data acquired during the performance of an approved ancillary study upon request.

2. Data sharing

The ancillary study investigator or the NASH CRN Steering Committee member serving as the liaison between the NASH CRN and the ancillary study are responsible for providing data files including new data (raw or processed) obtained from an ancillary study such as biomarkers measured

in NASH CRN serum, plasma, cDNA samples or genomic data generated from NASH CRN DNA samples. NASH CRN specimens, i.e., serum, plasma, cDNA, or DNA samples, will be provided to the ancillary study investigators under the condition that funding and analytical capabilities are secured to start the ancillary study within 3 months, and analyses must be completed within 6 months of receipt of the specimens. Assay results or data obtained from the ancillary study analyses will be made available within one year of completion to the NASH CRN for incorporation into the database for use by other investigators. NASH CRN clinical information on study participants will be provided to the ancillary study investigator or liaison after all raw or processed data generated through the ancillary study are returned to the NASH CRN Data Coordinating Center. Any data (raw or processed) provided to conduct an approved ancillary study may only be used in the manner in which the NASH CRN Ancillary Studies Committee and the NIDDK has approved (see Section 12. Appendices, for the template NIDDK Central Repositories Sample and Data Use Certification).

A written progress report that outlines data analysis results must be provided to the NASH CRN SC every six months. A final report outlining study results must be sent to the NASH CRN SC at the completion of the project. Any manuscripts or abstracts for professional society meetings (see section 7) resulting from usage of NASH CRN specimens must be reviewed by the Publications and Presentations Committee and the NASH CRN must receive credit for all presentations and publications resulting from usage of the NASH CRN specimens.

3. Definition of an ancillary study

An ancillary study is defined as a study that uses NASH CRN patients and/or data and biological specimens collected from them for a purpose other than intended by the NASH CRN and/or written into its protocols and procedures. In general, ancillary studies are characterized as being outside the specific scientific objectives of the NASH CRN studies, requiring a separate consent form, placing an additional burden on participants, and being funded by a funding mechanism that is separate from the NASH CRN funding mechanisms. An ancillary study may require new data collection (i.e., additional to that required by the NASH CRN) from NASH CRN patients, such as a new questionnaire for NASH CRN patients to complete, or a new biologic specimen to obtain from NASH CRN patients. Or, it might involve a new measurement on existing NASH CRN specimens. An ancillary study may involve all NASH CRN patients or NASH CRN patients at one or several NASH CRN sites. Examples of potential NASH CRN ancillary studies include collecting new, obesity-related data in the NASH CRN population, running assays on serum, plasma, cDNA samples, or genomic analyses on DNA samples.

An ancillary study may not use the central resources of the NASH CRN (e.g., central repository, Data Coordinating Center) for ancillary study purposes unless such use is agreed upon by the central resource and is supported by funding from the ancillary study. The ancillary study must make its own arrangements for whatever repository, data collection, management, and analysis support that it needs. An ancillary study should not interfere with or duplicate activities of a main study (e.g. PIVENS, TONIC, NAFLD Database, Adult NAFLD Database 2, or Pediatric NAFLD Database 2), a substudy, an existing ancillary study, or pilot and feasibility study. NASH CRN investigators or liaisons proposing an ancillary study will be required to sign a statement attesting that they have thoroughly reviewed all existing studies (available on the NASH CRN website) for conflict with the proposed study and have identified none. It behooves investigators finding potential conflicts to discuss them with the NASH CRN liaison before signing that there are none. If, after a study is completed, overlap with an existing study is identified (see Section 7, for publication requirements), permission to publish results may be denied.

4. Implementing an ancillary study

Investigators wishing to conduct an ancillary study must complete a study proposal (SP) form application. The NASH CRN Ancillary Studies Committee will review the application for scientific merit (using the expertise represented by the Committee) and will assess whether the ancillary study represents undue burden for NASH CRN patients or could interfere with completion of the NASH CRN objectives. The Ancillary Studies Committee will make a recommendation to the NASH CRN Steering Committee as to whether the ancillary study should be approved; the NASH CRN Steering Committee must approve the ancillary study for it to proceed. Investigators who are responding to a program announcement or applying for funding should gain NASH CRN approval for the ancillary study before submitting their application to a funding organization. An ancillary study may be proposed by investigators outside of the NASH CRN; however, in that case, at least one NASH CRN Steering Committee member must agree to serve as the liaison between the NASH CRN and the ancillary study investigator(s).

5. Procedure for proposing an ancillary study

An ancillary study is proposed to the NASH CRN by submission of a completed NASH CRN Ancillary Study Proposal (SP) form to the Ancillary Studies Committee in care of the Data Coordinating Center. This form is available on the open part of the NASH CRN website (www.nashcrn.com, click on Ancillary Studies).

Completion of this form will require specification of the following information:

- The principal investigator for the ancillary study and his/her institutional affiliation.
- Names of other key investigators for the ancillary study and their institutional affiliations.
- Name of the NASH CRN Steering Committee member who will be the liaison for the study.
- The study title, objective, and estimated start and end dates.
- A concept sheet describing the research design and methods for achieving the study objectives (2 page maximum length - this is to be a concise, well organized description).

- The NASH CRN resources which the ancillary study wishes to use:
  - New data or measurements that are to be collected on NASH CRN patients or specimens
  - Existing NASH CRN data that the study wishes to access
  - Number of patients involved
  - Quantity of specimens to be collected from patients and the conditions of specimen collection
  - If access to previously collected specimens is wanted for new measurements, the quantity and amount of specimens to be used should be specified
  - Frequency of visits or patient contacts or specimen collection
  - Types of interview questions or physical measures or data to be collected from patients
  - If access to previously collected NASH CRN data is requested (eg, measures on specimens or patients, treatment information), the nature of the requested data should be described
- The primary outcome variable and sample size, with justification.
- The funding source and status of funding for the ancillary study; any unreimbursed work or personnel time expected of the NASH CRN must be specified so that the Ancillary Studies Committee can evaluate whether the NASH CRN should assume that unreimbursed work or personnel time.
- The status of IRB approval and plans/procedures to protect patient confidentiality.
- An acknowledgment that the NASH CRN ancillary studies policy, including the policy on publications and presentations arising from ancillary studies, applies to the ancillary study.
- A signed statement attesting that the proposed study has no conflict or overlap with an existing study.

Each ancillary study must have the approval of the Principal Investigator at each NASH CRN site expecting to participate in the study.

The ancillary study activities that use NASH CRN resources may not proceed until the NASH CRN has approved the ancillary study.

6. Review process for proposed ancillary studies

A schedule of Ancillary Studies Committee meetings is posted on the NASH CRN website. Applications must be submitted to the Data Coordinating Center 3 weeks in advance of a meeting to be discussed at that meeting. The Data Coordinating Center will circulate the submitted ancillary study proposal (SP form) to the members of the Ancillary Studies Committee with instructions that they are to send their comments (see below for what they are to comment on) to the chairs of the Ancillary Studies Committee by a specified date (typically 1 week before the meeting or conference call at which it will be discussed). The principal investigator of the ancillary study and the NASH CRN liaison will each receive a copy of the memo directing the Ancillary Studies Committee to review the study proposal (SP form) so that they know the time frame for review. The chairs will collate the comments and prepare to discuss the application at the upcoming committee meeting. Upon completion of the discussion and vote of the Ancillary Studies Committee, the chairs will prepare a written memo to the Steering Committee specifying the Ancillary Studies Committee's recommendation for approval or disapproval. The Steering Committee will review that recommendation at their next meeting and make a decision for approval or disapproval. The principal investigator of the ancillary study and the NASH CRN liaison will each receive a copy of the memo from the Steering Committee specifying the decision for approval or disapproval.

Ancillary Studies Committee members will be asked to assess:

- Whether the study has sufficient scientific merit.
- Whether the study would interfere with other NASH CRN activities.
- Whether the study would hamper continued recruitment or participation in the NASH CRN.
- Whether the study is consistent with the NASH CRN aim of facilitating a broad range of research.
- Whether they recommend approval or disapproval of the study.

7. Publications, abstracts, and presentations arising from an ancillary study

Publications and abstracts arising from ancillary studies must be reviewed by the NASH CRN Presentations and Publications Committee prior to journal submission. The purpose of the review is to assure that any statements about the NASH CRN protocol are accurate and that the NASH CRN resources used in the ancillary study are appropriately acknowledged. Another purpose is to be sure that no conflict or overlap with existing or ongoing approved ancillary studies or proposed publications exists. The manuscript process will be:

- First, a proposal must be submitted in writing to the Presentations and Publications Committee by completion of the Abstract/Publication Proposal (PP) form. The P&P Committee will review the proposal prior to the submission of an abstract, presentation, or manuscript.
- The draft manuscript should be sent to the Presentations and Publications Committee in care of the Data Coordinating Center; the authors should specify the target journal.
- The paper will be circulated to the NASH CRN Steering Committee for voluntary comment.
- With the assistance of the DCC, the chairs of the Presentations and Publications Committee will identify an internal reviewer for the paper and send the paper to that individual with a deadline for response.
- The reviewer will review the paper for accuracy of statements about the NASH CRN resources used in the ancillary study, for appropriate acknowledgment of the NASH CRN, for overlap with other NASH CRN ancillary studies or publication proposals, and comment on any concerns about the validity of the data, its analysis, and the conclusions reached.
- The reviewer will send his/her review to the chair of the Presentations and Publications Committee.
- The result of the review may be that the manuscript is approved by the Steering Committee for submission to the NIDDK or that the manuscript needs revisions and further review.
- The final step in the NASH CRN internal review process is submission to NIDDK for review. All papers and abstracts arising from the NASH CRN, including ancillary study reports, must be reviewed by NIDDK prior to submission. The proposing investigator will submit the manuscript to the NIDDK representatives after receiving approval from the Presentations and Publications Committee to do so.
- The NIDDK project scientist will notify the Presentations and Publications Committee when the manuscript is approved for submission.
- If a dispute occurs between the authors and the Presentations and Publications Committee, resolution of the dispute is the responsibility of the Steering Committee.

If a manuscript is not accepted upon initial submission to a journal, the manuscript does not need to be re-reviewed by the NASH CRN after revision and prior to resubmission to a journal, unless there have been substantive changes to the statements that relate to NASH CRN resources or the acknowledgment of the NASH CRN. The ancillary study investigator will decide if re-review by the NASH CRN is needed.

Abstracts intended for national or international meetings (e.g., AASLD, DDW, EASL) must be reviewed by the NASH CRN Presentations and Publications Committee. The process for review of abstracts will be:

- Draft abstracts should be sent to the Presentations and Publications Committee in care of the Data Coordinating Center at least six weeks prior to the abstract submission deadline.
- Abstracts received after this deadline may be reviewed, if possible, but the Presentations and Publications Committee cannot guarantee to complete the review in time to meet the submission deadline.
- The abstract will be circulated to the Presentations and Publications Committee for review.
- The results of the review may be that the abstract is approved for submission, not approved for submission, or that it needs revision and second review by the Presentations and Publications Committee.
- The Data Coordinating Center, on behalf of the Presentations and Publications Committee, will notify the abstract authors of the decision made by the Presentations and Publications Committee at least three days before the abstract submission deadline.

Presentations (oral or poster) arising from ancillary studies will require approval by the NASH CRN liaison but will not require approval from the NASH CRN. However, the NASH CRN welcomes being informed about such presentations and would provide review of materials if requested. It is expected that any presentation from an ancillary study will include appropriate acknowledgment of the NASH CRN resources used by the ancillary study.

Authorship format should be proposed by the ancillary studies writing group and will be subject to review by the Presentations and Publications Committee; the format is expected to be either conventional (with an acknowledgment of the NASH CRN) or modified conventional (author list for the NASH CRN).

If during review of proposed publications overlap or conflict with ongoing NASH CRN investigations is discovered, permission to publish will be denied. It may be possible for an author/investigator to resolve the conflict by demonstrating that the results of the study advance the field by improving upon those of existing studies (i.e. a better methodology was used). It is the purview of the NASH CRN Steering Committee to resolve these issues and to oversee how the conflicting or overlapping results are presented in the manuscript in order to maintain the integrity of the NASH CRN.

Once an ancillary study is complete and published, all specimens should be destroyed and NASH CRN data files must be deleted (see sections 11.7 and 11.8). If sufficient specimens remain to perform additional examinations or measurements, the investigator may consider using them or sharing them with other investigators. However, plans for additional analyses must be submitted to the Ancillary Studies Committee for approval before such studies are initiated (see section 11.7).

8. Ancillary Studies Committee charge

The Ancillary Studies Committee does the following:

- Develops the policy for review and approval of ancillary studies of the NASH CRN.
- Reviews applications for ancillary studies of the NASH CRN and makes recommendations for approval or disapproval to the Steering Committee.
- Maintains a list of all proposed ancillary studies indicating approval status and the liaison. For approved studies, the list will indicate initiation date and the NASH CRN centers participating in the ancillary study.
- Maintains a list of allocations or commitments of existing or future NASH CRN samples to central NASH CRN and to ancillary studies.

The list of all proposed ancillary studies and the list of allocations and commitments of existing or future NASH CRN samples will be available on the closed portion of the NASH CRN website.

9. Ancillary Studies Committee membership, election, and voting

The Ancillary Studies Committee has 14 members: 2 chairpersons (initially appointed by the NIDDK and, thereafter, elected by the Steering Committee), 8 clinical center principal investigators or co-principal investigators (initially appointed by the NIDDK and, thereafter, elected by the Steering Committee), two representatives from the Pathology Committee (who share one vote), one investigator from the Data Coordinating Center, and a NIDDK representative. The chairpersons and 8 members from the clinical centers serve for 2-year terms. Terms for the initially appointed chair and members will run for 2 years from the date of the initial study review conducted by the committee. The members from the Pathology Committee, the Data Coordinating Center, and NIDDK serve for the duration of the NASH CRN. Members and chairs may serve unlimited terms if elected.

The Data Coordinating Center will coordinate the election process. Steering Committee members will be queried for their interest in being on the committee. A ballot with their names will be circulated for a mailed vote by Steering committee members. There will be separate elections for chairperson and for committee members. In the case of tie votes, the Executive Committee will decide the issue.

If an Ancillary Studies Committee member proposes an ancillary study, collaborates on an ancillary study, or is affiliated with the institution of an investigator who proposes an ancillary study, he/she will be excused from reviewing and voting on that ancillary study proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest.

10. Ancillary Studies Committee operation

The Ancillary Studies Committee is a subcommittee of the NASH CRN Steering Committee. The NASH CRN Data Coordinating Center supports the operations of the Ancillary Studies Committee by arranging Committee conference calls, receiving submitted applications for ancillary studies, administering the process for review of submitted applications, writing correspondence for the Committee, maintaining the lists of ancillary studies and allocated or committed samples, and archiving the correspondence files relating the Committee's activities. The Data Coordinating Center relies on the named Steering Committee member liaison and proposing investigator for each ancillary study and the Ancillary Study Committee members in completion of these activities.

11. Miscellaneous issues

11.1. Receipt dates for study proposals

The deadlines for receipt of ancillary study proposals for review by the NASH CRN Ancillary Studies Committee are 1 February, 1 June, and 1 October. Proposals received by 1 February of each year will be reviewed and the proposer notified of the decision by 31 March. Similarly, proposals received by 1 June will be reviewed and the proposer notified by 31 July, and proposals received by 1 October will be reviewed and the proposer notified by 30 November. These receipt dates allow notification of the applicant of the NASH CRN Steering Committee's approval or disapproval two months before the NIH due dates for funding applications for new projects.

11.2. Consent and IRB issues

Consent for the ancillary study cannot be part of any NASH CRN consent – ancillary studies are separate from the NASH CRN by definition. Therefore, each ancillary study must have its own consent form. Each site participating in an ancillary study must have approval from their IRB for participation in the ancillary study.

11.3. Funding issues

Ancillary studies are supported by non NASH CRN resources. Investigators proposing ancillary studies must seek funding from outside sources to conduct their research. Examples include funding obtained through investigator-initiated NIH research grant awards (R01s), program announcements, grants from academic institutions, or private sources (e.g., drug companies, non-profit health organizations). The NASH CRN Steering Committee can provide letters of support for applications for funding for ancillary studies approved by the NASH CRN. If funding is not approved, the letter of support may not be used for other applications. A revised ancillary study proposal should be submitted and a new letter of support will be provided. Conduct of ancillary studies must comply with all existing NASH CRN and NIH policies and guidelines.

If the application for an ancillary study states that it is to be submitted for funding by NIH or another federal source, it is understood that the data, specimens and other resources of the NASH CRN may not be used until a Notice of Grant Award is issued. If alternative funding is identified, a revised study proposal form may be submitted that describes the funding and how it will suffice to complete the proposed studies.

An ancillary study that wishes to use the services of the Data Coordinating Center or any other NASH CRN central resource may contact the principal investigator of that resource regarding participation in the ancillary study. Such participation has to be funded with non NASH CRN resources.

11.4. Expiration of NASH CRN approval

In general, approved ancillary studies must be initiated within one year of being approved, or the approval will be withdrawn; this will allow reallocation of resources reserved for an ancillary study that does not go forward, e.g., due to failure to obtain funding, relocation of the proposing investigator, or loss of interest in the proposed research. The principal investigator of the ancillary study and the NASH CRN Steering Committee liaison will each receive written notice 2 months before an ancillary study's approval is due to expire. The ancillary study investigator may appeal this expiration of NASH CRN approval, e.g., if a funding decision is pending or if an application for funding is being revised and resubmitted. The ancillary study investigator should send a letter requesting an extension of approval to the chair of the Ancillary Studies Committee. The letter should indicate the expected timeline for initiation of the ancillary study and describe the actions that are being taken to meet that timeline.

11.5. NASH CRN liaison

An ancillary study that is proposed by an investigator outside of the NASH CRN must have a NASH CRN liaison. This person must be a NASH CRN Steering Committee member. The liaison serves as the communications link between the Steering Committee and the ancillary study. For example, the liaison would provide status reports on the ancillary study at the Ancillary Studies Committee conference calls, at Steering Committee meetings, and would assist the Data Coordinating Center as needed in communicating with the ancillary study. The liaison may participate in the ancillary study but participation is not required.

11.6. Changes to an ancillary study's protocol

If a major change occurs to an ancillary study's protocol after it has been approved by the NASH CRN (eg, addition of a visit, addition of a specimen, or addition of a measurement on a NASH CRN specimen – something that affects the impact on the NASH CRN participant or resource used), the Ancillary Studies Committee must approve the change before it is implemented. The Steering Committee will be asked to approve the alterations, based on the recommendation of the Ancillary Studies Committee.

11.7. Use of and disposal of biological specimens provided from the NASH CRN repository

It is understood that specimens provided by the NASH CRN for an ancillary study are to be used only for the purpose expressly detailed in the proposal. If an investigator discovers a new use for them, no matter how potentially valuable and timely to an emerging field of study, s/he must submit a new ancillary study proposal detailing the proposed use, which will undergo full review. Failure to comply with this requirement will certainly result in denial of permission to publish the results of the study.

It is the responsibility of the ancillary study investigator (and NASH CRN liaison if the investigator is not a member of the Steering Committee) to dispose of specimens upon completion of the ancillary study for which they were acquired, if the investigators do not plan to submit a new ancillary study to extend the use of the samples. The time of completion of the study will be taken as the date of publication of the results of the study. The specimens are to be disposed of and the investigator (and liaison if applicable) will be asked to certify this in writing within 6 months of the publication date. The method of disposal should be in accordance with the biosafety committee (or similar agency) of the investigator's institution.

In some instances the proposed studies will not be completed (i.e. results will not be published), in which case the specimens may not be held indefinitely. A period of 2 years from the date of distribution of the specimens to the investigator is taken as reasonable to complete the study. The specimens are to be disposed of and the investigator (and liaison if applicable) will be asked to certify this in writing within 2 years and 3 months of the date of specimen distribution. That is unless the investigator has applied to the NASH CRN for an extension and has received approval for holding the specimens for some amount of time (to be prescribed in the application and approval, but not to exceed 2 years). The date by which specimens are to be disposed of then moves forward to 3 months after the extension date or completion of the study, whichever comes first. Investigators may not apply for a second extension.

Specimens may not be returned to the NASH CRN repository under any circumstances. The NASH CRN has determined that the quality of the specimens cannot be assured once they have been in the hands of an entity other than the NIDDK central repositories. If for some reason the specimens have not been used, their use does not deplete them, or residuals are sufficient to perform additional studies, it is considered responsible behavior on the part of the investigator to find use for them. Possible uses include additional studies by the investigator or studies by other investigators. Any such use is governed by the NASH CRN in the same way the primary use has been. Application must be made for an ancillary study by the process described above. If approval is given to use the samples, the NASH CRN takes no responsibility for assuring their distribution or for their quality. Publication of results and other activities of secondary ancillary studies are governed by the NASH CRN exactly as are activities of primary ancillary studies.

11.8. Use of and destruction of data provided from the NASH CRN DCC

It is understood that data provided by the NASH CRN for an ancillary study are to be used only for the purpose expressly detailed in the proposal. If an investigator discovers a new use for them, no matter how potentially valuable and timely to an emerging field of study, s/he must submit a new ancillary study proposal detailing the proposed use, which will undergo full review. Failure to comply with this requirement will certainly result in denial of permission to publish the results of the study.

It is the responsibility of the ancillary study investigator (and NASH CRN liaison if the investigator is not a member of the Steering Committee) to make good-faith effort to permanently delete all NASH CRN data files and associated derived electronic data files upon completion of the ancillary study for which they were acquired. The time of completion of the study will be taken as 6 months from the date of publication of the primary results of the study. It is the responsibility of the investigator (and liaison if applicable) to certify the completion of the data file deletion and to affirm that no further use of the data for any purpose will be made. This communication should be done in an email directed to the NASH CRN Data Coordinating Center. If further use of the data for any purpose is desired, permission must be requested from the Presentations and Publications Committee not later than 3 months after publication of the primary results paper, which must be accompanied with a new Publication Proposal.

11.9. Confidentiality

Confidentiality of individually identifiable data about NASH CRN participants must be assured. The NASH CRN provides no assurances that ancillary studies will be able to identify and contact NASH CRN participants in the future, particularly after the NASH CRN ends.

Acknowledgments:
In drafting the NASH CRN Ancillary Studies Policy, we referred to the following sources: Ancillary Studies policies of the Virahep-C, HALT-C, BARC, and CLiC studies sponsored by the NIDDK, and the National Emphysema Treatment Trial sponsored by the NHLBI

2.4. Genetics committee

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   - **F. Example of non-PLINK Codebook Directory**
   - **G. Example of non-PLINK Codebook Data Upload**

1. Genetics Committee charge

The Genetics Committee is a subcommittee of the NASH CRN Steering Committee. The Genetics Committee will act in a supportive role to the NASH CRN Ancillary Studies Committee and Presentations & Publications Committee in the following manner:

1) Develop policies with regards to
   (a) releasing NASH CRN genomic data to NASH CRN and non-NASH CRN investigators for genetics ancillary studies
   (b) proper use of NASH CRN's biosamples, including DNA, following its release to the investigators
   (c) disposition of NASH CRN's biosamples following the completion of the genetics ancillary study
   (d) submitting raw genetics data back to the NASH CRN [the specifics of when, in what form, to whom are outlined below] and to the public domain.

2) Assist the Ancillary Studies Committee by reviewing the genetics ancillary studies or ancillary studies with a genetic component. The Ancillary Studies Committee will remain primarily responsible for the review and approval of the genetics ancillary studies but one of the reviewers (or both) will come from the Genetics Committee as determined by the Ancillary Studies Committee chairs.

3) Assist the Presentations and Publications Committee by reviewing the genetics ancillary study publications or other publications with a genetic component. The Presentations and Publications Committee will remain primarily responsible for the genetics ancillary study publications but one of the reviewers (or both) will come from the Genetics Committee as determined by the Presentations and Publications Committee Co-Chairs.

2. Implementing genetics ancillary studies

Investigators wishing to conduct a genetics ancillary study must complete a NASH CRN Study Proposal (SP) form. The NASH CRN Ancillary Studies Committee in collaboration with the Genetics Committee will review the application for scientific merit (using the expertise represented by the Committee) and will assess whether the ancillary study represents undue burden for NASH CRN patients or could interfere with completion of the NASH CRN objectives. The Ancillary Studies Committee will make a recommendation to the NASH CRN Steering Committee as to whether the ancillary study should be approved; the NASH CRN Steering Committee must approve the genetics ancillary study for it to proceed. Investigators who are responding to a program announcement or applying for funding should gain NASH CRN approval for the genetics ancillary study before submitting their application to a funding organization. A genetics ancillary study may be proposed by investigators outside of the NASH CRN; however, in that case, at least one NASH CRN Steering Committee member must agree to serve as the liaison between the NASH CRN and the genetics ancillary study investigator(s). The process for reviewing genetics ancillary studies is as follows:

1) Ancillary Studies Committee Co-Chairs assign one Ancillary committee member and one Genetics Committee member to review the genetics ancillary study proposal.
2) Reviewers decisions are discussed at Ancillary Studies Committee meeting, where the proposal is recommended for approval, conditional approval or disapproval or referral to the Genetics Committee
3) If referred to the Genetics Committee for full review, then the proposal is discussed at Genetics Committee meeting, where the proposal is either recommended for approval or disapproval.
4) Once the Ancillary Studies Committee or the Genetics Committee has reached a decision, the proposal is sent to Steering Committee for final approval or disapproval.

3. Background and access to NASH CRN specimens

The NASH CRN studies comprise a large and well characterized population sample of adults and children with various stages of nonalcoholic fatty liver disease, including steatosis, steatohepatitis, and NASH-related cirrhosis. To make the best possible use of this extraordinary resource, the NASH CRN encourages external investigators, as well as NASH CRN investigators, to develop genetics ancillary studies.

Access by genetics ancillary studies to NASH CRN specimens and data collected on participants will be governed by the NASH CRN Steering Committee and administered by the Data Coordinating Center. It is likely that access to baseline specimens and data from a NASH CRN study will be permitted to a genetics ancillary study prior to the conclusion of the NASH CRN study, but only after the NASH CRN has determined that the baseline data are of a quality suitable for sharing. Follow-up specimens, data, and information about treatment assignment in a NASH CRN clinical trial are unlikely to be available until after the NASH CRN trial has ended, regardless of the timing of the genetics ancillary study. Genetics ancillary study investigators should be aware that there may be delays of possibly years before NASH CRN data are released.

Data and biosamples collected using NASH CRN central resources are governed by the NASH CRN Steering Committee; these are NASH CRN data and NASH CRN biosamples. The NASH CRN specimens and clinical data are provided to the genetics ancillary study investigator with the understanding that all biomarker and genomic data generated through the genetics ancillary study will be shared by the NASH CRN. Other measurements made on NASH CRN samples under an approved ancillary study protocol and paid for by ancillary study resources may be retained for the sole use of the investigator in publishing or Intellectual property purposes as deemed appropriate. However, the NASH CRN must be granted access to all genomic data acquired during the performance of an approved genetic ancillary study upon request.

4. Genomic data specifications

The genetics ancillary study investigator or the NASH CRN Steering Committee member serving as the liaison between the NASH CRN and the ancillary study is responsible for providing genomic data files including new data (raw or processed) obtained from a genetics ancillary study back to the NASH CRN.

NASH CRN specimens, i.e., serum, plasma, cDNA, or DNA samples, will be provided to the genetics ancillary study investigators under the condition that funding and analytical capabilities are guaranteed at the time of receiving the samples and that analyses will be completed within 6 months of receipt of the specimens. Genomic results or data obtained from the genetics ancillary study analyses will be made available within one year of completion to the NASH CRN for incorporation

into the database for use by other investigators. NASH CRN clinical information on study participants will be provided to the genetics ancillary study investigator or liaison after all raw or processed data generated through the ancillary study are returned to the NASH CRN Data Coordinating Center. Any data (raw or processed) provided to conduct an approved genetics ancillary study may only be used in the manner in which the NASH CRN Ancillary Studies Committee in collaboration with the Genetics Committee and the NIDDK has approved.

A written progress report that outlines data analysis results must be provided to the NASH CRN SC every six months. A final report outlining study results must be sent to the NASH CRN SC at the completion of the project. Any manuscripts or abstracts for professional society meetings resulting from usage of NASH CRN specimens must be reviewed by the Presentations and Publications Committee in collaboration with the Genetics Committee and the NASH CRN must receive credit for all presentations and publications resulting from usage of the NASH CRN specimens.

All genomic data should be submitted to the NASH CRN in PLINK format, with the accompanying MAP files. PLINK is free, open-source whole genome association analysis toolset, designed to perform a range of basic, large-scale analyses in a computationally efficient manner. For more information about using and downloading PLINK please go to http://pngu.mgh.harvard.edu/~purcell/plink/contact.shtml.

5. Use and disposal of NASH CRN biological specimens

It is understood that specimens provided by the NASH CRN for a genetics ancillary study are to be used only for the purpose expressly detailed in the proposal. If an investigator discovers a new use for them, no matter how potentially valuable and timely to an emerging field of study, s/he must submit a new genetics ancillary study proposal detailing the proposed use, which will undergo full review. Failure to comply with this requirement will result in denial of permission to publish the results of the study.

It is the responsibility of the genetics ancillary study investigator (and NASH CRN liaison if the investigator is not a member of the Steering Committee) to dispose of specimens upon completion of the ancillary study for which they were acquired if the investigators do not plan to submit a new ancillary study to extend the use of the samples. The time of completion of the study will be taken as the date of publication of the results of the study. The specimens are to be disposed of and the investigator (and liaison if applicable) will be asked to certify this in writing within 12 months of the publication date. The method of disposal should be in accordance with the biosafety committee (or similar agency) of the investigator's institution.

In some instances the proposed genetics ancillary studies will not be completed (i.e. results will not be published), in which case the DNA specimens may not be held indefinitely. A period of 2 years from the date of distribution of the specimens to the investigator is determined as reasonable to complete the proposed genetics ancillary study. The specimens are to be disposed of and the investigator (and liaison if applicable) will be asked to certify this in writing within 2 years and 3 months of the date of specimen distribution, unless the investigator has applied to the NASH CRN for an extension and has received approval for holding the specimens for some amount of time (to be described in the application and approval, but not to exceed additional 2 years). The date, by which specimens are to be disposed of then moves forward to 3 months after the extension date or completion of the study, whichever comes first. **Investigators may not apply for a second extension.**

Specimens may not be returned to the NASH CRN genetics and biosample repository under any circumstances. The NASH CRN has determined that the quality of the specimens cannot be assured once they have been in the hands of an entity other than the NIDDK central repositories.

6. Use and deletion of NASH CRN data

It is understood that data provided by the NASH CRN for a genetics ancillary study are to be used only for the purpose expressly detailed in the proposal. If an investigator discovers a new use for them, no matter how potentially valuable and timely to an emerging field of study, s/he must submit a new genetics ancillary study proposal detailing the proposed use, which will undergo full review. Failure to comply with this requirement will result in denial of permission to publish the results of the study.

It is the responsibility of the genetics ancillary study investigator (and NASH CRN liaison if the investigator is not a member of the Steering Committee) to make good-faith effort to permanently delete all NASH CRN data files and associated derived electronic data files upon completion of the ancillary study for which they were acquired. The time of completion of the study will be taken as 12 months from the date of publication of the primary results of the study. It is the responsibility of the investigator (and liaison if applicable) to certify the completion of the data file deletion and to affirm that no further use of the data for any purpose will be made. This communication should be done in an email directed to the NASH CRN Data Coordinating Center. If further use of the data for any purpose is desired, a new Publication Proposal must be submitted and permission must be requested from the Presentations and Publications Committee no later than 3 months after publication of the primary results paper.

7. Genetics ancillary study publications, abstracts, and presentations

Investigators wishing to present the results of a genetics ancillary study to a society meeting or journal must complete an NASH CRN Abstract/Publication Proposal (PP) form. Publications and abstracts arising from genetics ancillary studies must be reviewed by the NASH CRN Presentations and Publications (P&P) Committee in collaboration with the Genetics Committee prior to submission. The purpose of the review is to assure any statements about the use NASH CRN data are accurate and the NASH CRN resources used in the genetics ancillary study are appropriately acknowledged. Another purpose is to be sure that no conflict or overlap with existing or ongoing approved genetics ancillary studies or proposed publications exists. The process for reviewing genetics ancillary studies is as follows:

1) P&P Committee Co-Chairs assign one P&P committee member and one Genetics Committee member to review the publication proposal.
5) Reviewers decisions are discussed at P&P Committee meeting, where the proposal is recommended for approval, conditional approval or disapproval or referral to the Genetics Committee
2) If referred to the Genetics Committee for full review, then the proposal is discussed at Genetics Committee meeting, where the proposal is either recommended for approval or disapproval.
3) Once the P&P Committee or the Genetics Committee has reached a decision, the proposal is sent to steering committee for final approval or disapproval

Manuscripts intended for publication must be reviewed by the NASH CRN Presentations and Publications Committee and Genetics Committee. If a manuscript is not accepted upon initial submission to a journal, the manuscript does not need to be re-reviewed by the NASH CRN after revision and prior to resubmission to a journal, unless there have been substantive changes to the statements that relate to NASH CRN resources or the acknowledgment of the NASH CRN. The genetics ancillary study investigator will decide if re-review by the NASH CRN is needed.

Abstracts intended for national or international meetings (e.g., AASLD, DDW, EASL) must be reviewed by the NASH CRN Presentations and Publications Committee and the Genetics Committee.

Power point Presentations or posters arising from genetics ancillary studies will require approval by the NASH CRN liaison but will not require approval from the NASH CRN. However, the NASH CRN welcomes being informed about such presentations and would provide review of materials if requested. It is expected that any presentation from a genetics ancillary study will include appropriate acknowledgment of the NASH CRN resources used by the genetics ancillary study.

Authorship format should be proposed by the genetics ancillary studies writing group and will be subject to review by the Presentations and Publications Committee and the Genetics Committee; the format is expected to be either conventional (with an acknowledgment of the NASH CRN) or modified conventional (author list for the NASH CRN).

If overlap or conflict with ongoing NASH CRN investigations is discovered during the review of proposed publications, permission to publish will be put on hold pending adjudication or may be denied. It may be possible for an author/investigator to resolve the conflict by demonstrating that the results of the study advance the field by improving upon those of existing studies (i.e. a better methodology was used). It is the purview of the NASH CRN Genetics Committee to resolve these issues and to oversee how the conflicting or overlapping results are presented in the manuscript in order to maintain the integrity of the NASH CRN.

8. Appendices

- **A. NASH CRN Study Proposal Form (SP)**
- **B. NASH CRN Abstract/ Publication Proposal Form (PP)**
- **C. PLINK: Basic usage/ data format**
- **D. Example of PLINK map file**
- **E. Example of PLINK GWAS dataset**
- **F. Example of non-PLINK Codebook Directory**
- **G. Example of non-PLINK Codebook Data Upload**

2.5. Dissemination of information

Categories of information about the study

- Information currently in the public domain
- Privileged information (ie, dissemination limited to the study investigators): minutes, meeting materials, draft documents, data reports
- Information disseminated by the participating centers

Release of information

- As the study progresses, information will be released to the public domain, but the release is subject to Steering Committee approval

Information about the study may be directed at

- Potential patients
- Medical community referral sources (physicians, hepatic or gastroenterology associations, etc.)
- Public relations with the lay community or scientific community
- Scientific community in general

Information directed at potential patients, at referral sources, or produced for public relations purposes

- Should not be advertisements for a particular treatment
- Should emphasize the following points:
  - The study represents a collaborative effort involving multiple centers
  - The local center is only one center in the study
  - The study is sponsored by the NIDDK
  - The trials are being done because it is not known which treatment is better
  - The trials are ongoing and will take a period of time to address the questions
  - Results will not be available until published by the Steering Committee
- Should be limited to efforts to enhance recruitment of patients
- All publicity for recruitment purposes requires IRB approval prior to implementation
- Each clinic should keep a record and copies of local publicity (letters, press releases, flyers, scripts for radio or TV advertisements, etc.) for review during site visits or other requested

Information disseminated at scientific meetings

- This falls under the presentation policy

2.5. Dissemination of information

Strategies for dealing with requests for information

- Personnel at each center should refer any requests from the news media for information on the study to the principal investigator
- Any principal investigator asked to supply information on the study at a local level should emphasize the following points:
  - The study represents a collaborative effort involving multiple centers
  - The local center is only one center in the study
  - The study is sponsored by the NIDDK
  - The trials are being done because it is not known which treatment is better
  - Results will not be available until released by the NIDDK
- Principal investigators should refer all inquiries concerning the study dealing with information not in the public domain to the Study Co-chairs

2.6. Availability of data

Data available to NASH CRN investigators e.g., during the course of a study

- Performance data (e.g., related to recruitment, data management, adherence to protocol, conduct of study procedures)
- Baseline data characterizing the study population
- Limited follow-up data (e.g., safety data) may be discussed with the study group during the course of a study
- During the course of a study, the study operates with a data and safety monitoring board that is responsible for review of accumulating data

Data available to study group upon close of a study

- Follow-up data by treatment group

Availability of data to public

- Study data of any kind are not available outside the NASH CRN investigators until release is approved by the Steering Committee and NIDDK

2.7. List of study documents

- CyNCH protocol
- CyNCH Forms and Flashcards
- CyNCH consents and assents
- NASH CRN Policy and Procedures Memoranda
- CyNCH Standard Operating Procedures
  - Part I: Clinical Center Operations
  - Part II: Administrative
  - Part III: Web Based Data Management System
  - Part IV: Liver Biopsy and NAFLD Histology Scoring System
  - Part V: Standard of Care for adult patients with fatty liver disorders
  - -- Part VI: MRI Procedure Manual

NASH CRN

Nonalcoholic Steatohepatitis

Clinical Research Network

Standard Operating Procedures

Part III: NASH CRN Web-Based Data Management System

for

NAFLD Database 2
CyNCh
FLINT

26 April 2012

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1. Introduction

The major functions of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) web-based data management system are:

- Registration of new participants into a study or trial of the NASH CRN.
- Data entry of forms.
- Inventory of forms keyed for each participant.
- Eligibility checking and enrollment or randomization.
- Printing blank forms and visit labels,
- Printing listings of visit window schedules, visits due, missing forms, etc.
- Staff training in the functions of the data system using the tutorial system application.
- Certification of data system users via the tutorial system application.

This data system is **not** a replacement of the original data collection forms. Participant data **must** be recorded onto the paper data collection forms before entry of the form data into the electronic database may be done.

Use of the NASH CRN data system for purposes other than those described in this manual is prohibited unless permission is received from the Data Coordinating Center (DCC).

The data system is Internet-based. Any computer with Internet Explorer with the settings described in section 2.1 can be used to log into the NASH CRN data system and to use any of the system's functions, including data entry of forms.

Security precautions must be taken at all times to protect the integrity of the data system and maintain confidentiality of participant data. For example,

- Verify that the computer's Internet Explorer version and settings are correct before accessing the system.
- Use only the Personnel Identification Number (PIN) assigned to you by the DCC and your authorized password.
- Do not share your password.
- Use precautions so that any forms taken off-site are not lost or shared with outsiders.
- NEVER send any participant identification information to the DCC.
- Always key form data EXACTLY as written on the form.

The system is robust to most problems. Checks have been built in to monitor the integrity of the data (e.g., checks to avoid duplication of data, miskeys of ID information) and to minimize vulnerability of files to damage. You should feel secure in your use of the system, even as you are learning.

If any problems occur while using the data system or if you ever see error messages that you cannot resolve (e.g., data system script errors), leave the system as is, either print the screen with the error or save the image to a file, and e-mail at least 2 DCC staff members or call the DCC at 410-955-8175 immediately.

2. Getting started

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2.1. Operating System and Internet Explorer requirements

The data system can be accessed from any PC with a Microsoft Windows Operating System and Internet Explorer web browser preferably updated to version 7.0 or higher. The data system functions through the Internet Explorer browser. No other browsers may be used with the NASH CRN data system for consistency and security reasons. Before using the system, ensure that the PC's Operating System (OS) and version and settings on Internet Explorer are correct.

1. Establish that there is an Internet connection.
   - Contact your IT department if you do not have an Internet connection.

2. Determine which Operating System is being used.
   - From the desktop, right-click on 'My Computer', then 'System Properties'.
   - The OS and service pack (SP) are given under the General tab.
   - Contact your IT department if you do not have either Microsoft Windows Operating System XP Service Pack 2 (or higher) or Windows 7. The data system will function on a Windows OS prior to XP, but for reasons of maximum security and consistency, XP or higher is suggested.

3. Determine which Internet Explorer version and service pack (SP) are being used.
   - From the desktop, open Internet Explorer by double clicking on the icon.
   - Click on *Help*, then *About Internet Explorer*.
   - The pop-up window information gives the version and service pack (SP) in use.

4. Download Internet Explorer Version 8 (IEv8) if not previously installed. (not required if you have IEv7)
   - Go to http://www.microsoft.com/windows/downloads/default.mspx.
   - Click on "Download Internet Explorer 8 today" located at top center of page.
   - Follow the instructions to download Internet Explorer 8.
   - Accept all defaults.
   - Restart your PC after installation.

5. Enable Error Notification in Internet Explorer.
   - From the desktop, open Internet Explorer by double clicking on the icon.
   - Click on *Tools*, then *Internet Options*.
   - Select the Advanced tab.
   - Click in the box labeled *"Display a notification about every script error*" located under "Browsing".
   - Click on *Apply*, then *OK*.

6. To access the data system, open the NASH CRN website http://jhuccs1.us/nash/ in Internet Explorer and click on *Data System* (at the left side of the home page).

7. Set the POP-UP blocker to OFF for the NASH CRN website. In Internet Explorer:
   - Click on *Tools*, then *Internet Options*.
   - Select the Privacy tab.
   - Click *Settings* under 'Pop-Up Blocker' at bottom of tab.
   - Type : http://jhuccs1.us/nash in the space under "*Address of Website to allow*".
   - Click *Add*, then *Close*, then *Ok*.

8. **Optional**: Set the NASH CRN website as your home page. In Internet Explorer,
   - Click on *Tools*, then *Internet Options*.
   - Select the General tab and type http://jhuccs1.us/nash in the address window for the Home page.
   - Click on *OK*.

9. Most sections of the NASH CRN website are password protected. The DCC will periodically change the password and will send an e-mail notification prior to the change. The username for the NASH CRN website is: nashcrn. Note that the Data System has a different username and password (section 2.3).

2.2. Monthly maintenance

The Internet is a dynamic environment. Personal settings and use of the Internet for non-data entry activities sometimes unintentionally and unknowingly change the Internet Explorer settings. Anti-virus software should be updated and run daily. At least once a month, the following tasks need to be done to help prevent these changes from affecting the NASH CRN data system:

1. Delete temporary Internet files.
   - Open Internet Explorer.
   - Click on *Tools*, then *Internet Options*.
   - Select the General tab.
   - Click on the *Delete* button under Browsing history.
   - Click on the box "*Delete all offline content"* or click on "*Delete files*".
   - Click on *OK*, then *Close*.

2. Check enable error notification.
   - Click on *Tools*, then *Internet Options*.
   - Select the Advanced tab.
   - If there is NOT a check in the box labeled "*Display a notification about every script error"* under "Browsing", then click on the box, then *Apply*, then *OK.*

3. Verify that the POP-UP blocker is set to OFF for the NASH CRN website.
   - Click on *Tools*, then *Internet Options*.
   - Select the Privacy tab.
   - Click *Settings* under "Pop-up Blocker" at bottom of tab.
   - If http://jhuccs1.us/nash is not displayed in space under "*Address of Website to allow,*" then key this website address, click on *Add*, then *Close.*

4. Run anti-virus software.

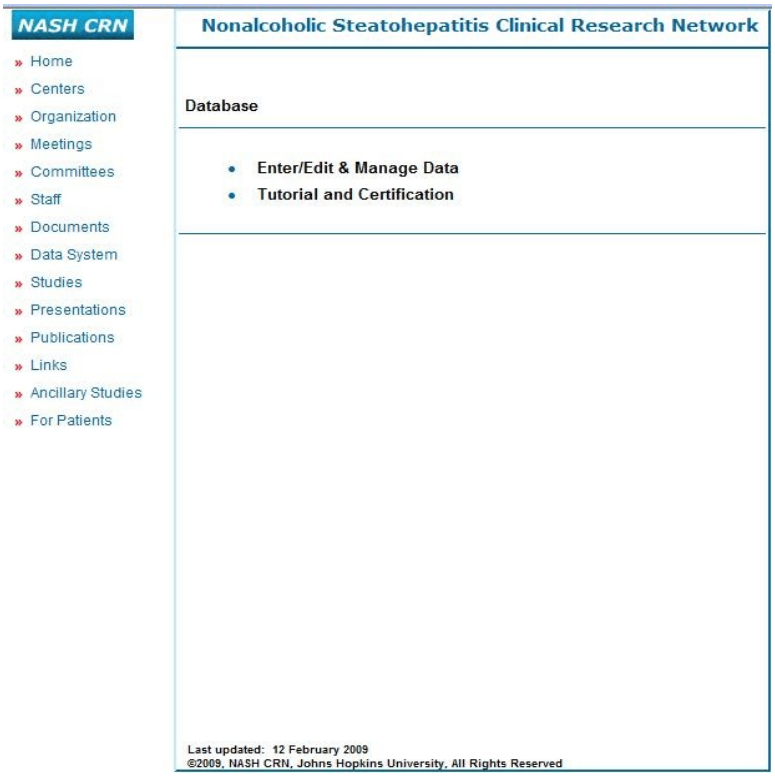
5. Run spyware detection software. Freeware such as AD-Aware and SPYBOT can be downloaded from www.download.com.

2.3. Log-in procedures

Note that only one person per clinic per study or trial may key forms in the data system at a time, so verify that no other users are logged on working in the same study before beginning your session.

Go to the NASH CRN website (http://jhuccs1.us/nash) and select *Data System* from the menu on the left to view the Database home page. There are two options. Select either *Enter/Edit & Manage Data* or *Tutorial and Certification* (see figure 2.3a). Until the tutorial has been completed and you become certified for data entry, you will not have access to the first option.

2.3a Database home page and initial log-in (figure)

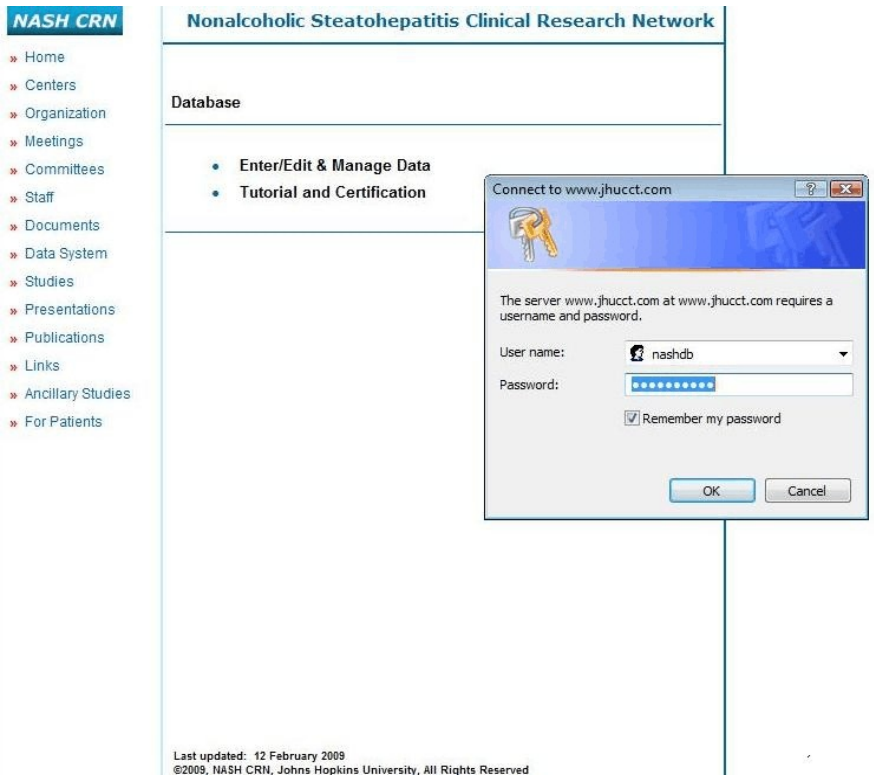


For either mode, the first thing to appear is the SIGN ON screen (see figure 2.3b). This is a universal log-in for all data system users. Be aware that the username and password are DIFFERENT than those used to access other non-public areas of the NASH CRN website (http://jhuccs1.us/nash).

- Type in:
  Username: **nashdb**
  Password: **keysmart11**

- Click on the *OK* button.

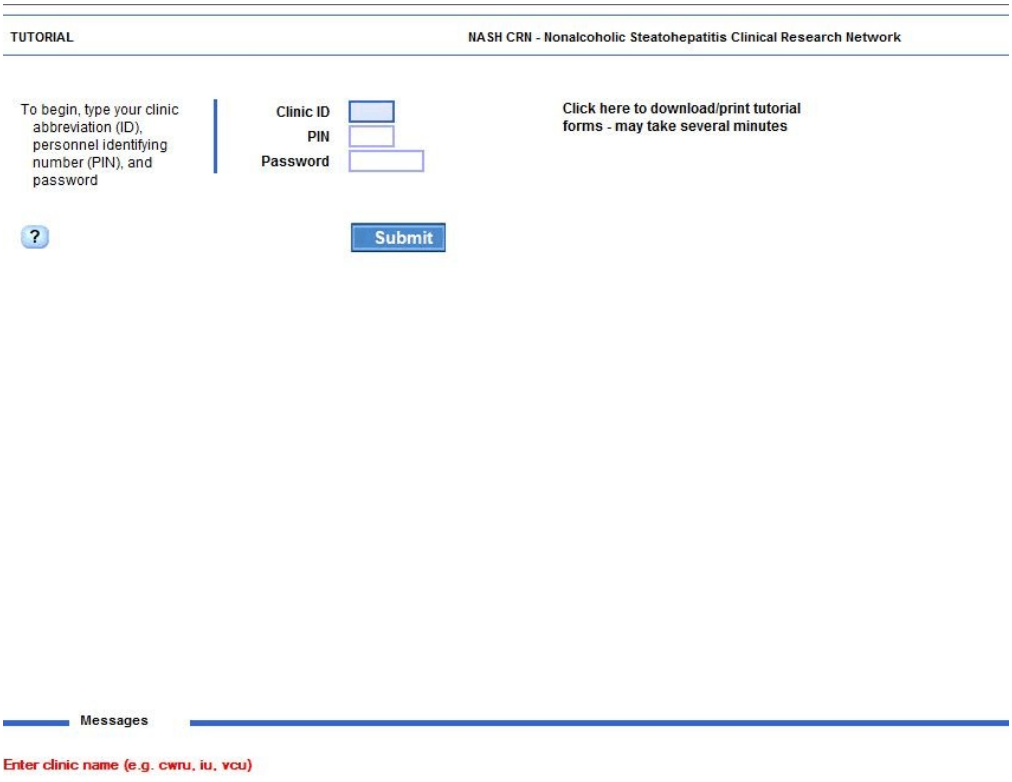
2.3b Data system sign on screen (figure)



The next screen for both the *Enter/Edit & Manage Data* and the *Tutorial and Certification* modes is a personal log-in page (see figure 2.3c). Type in your clinic's ID (see Appendix 11.1) and your unique Personnel Identification Number (PIN) and password.

Every data system user at your clinic must receive a unique PIN from the DCC, define their personal password, and become data entry certified. If a clinic staff member has already received a PIN from the DCC (e.g., when becoming certified as a Study Physician or Clinical Coordinator), use this PIN to become data entry certified. Obtaining a PIN and becoming certified is described in Chapter 3 (the tutorial) of this manual.

2.3c Personal log-in (figure)

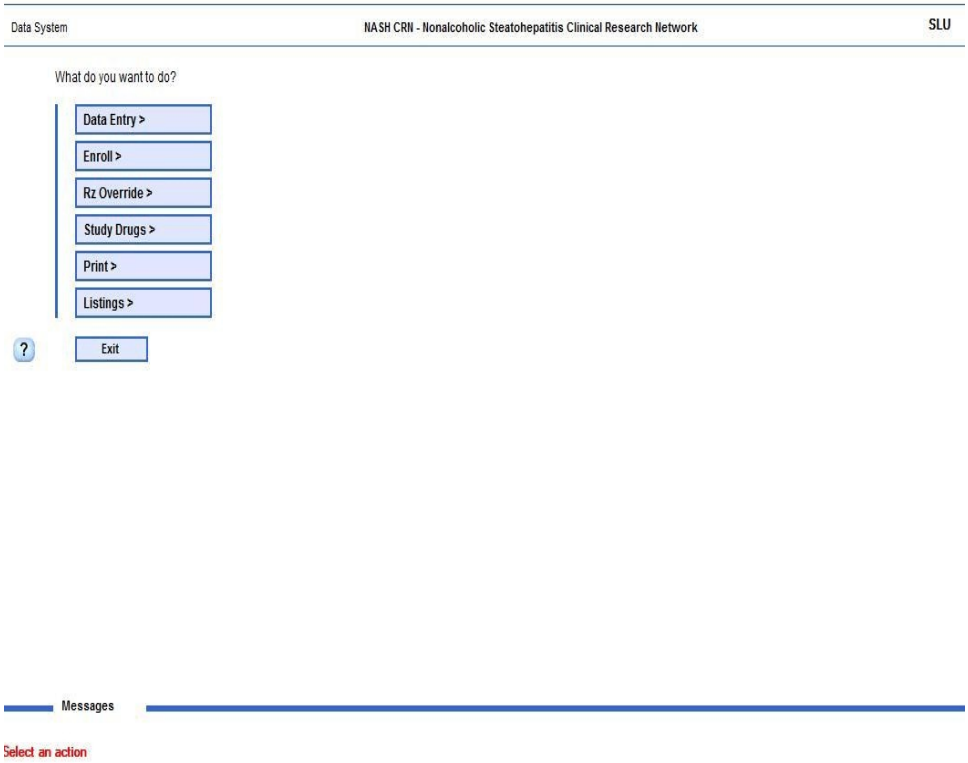


2.4. Layout description

The TASKS menu screen is the first screen after you are logged into the system for either the data management or tutorial modes. Figure 2.4a shows the MAIN TASKS menu for the *Enter/Edit & Manage Data* mode. It will be used to illustrate several features of the data system. Each screen is comprised of several sections:

- The **header** contains the Data System name, "NASH CRN - Nonalcoholic Steatohepatitis Clinical Research Network" and your clinic ID code on the right hand side.
- The **middle section** of the screen is where you can enter your selections or data. If available for the screen, a help icon will be located on the lower left of the screen. Click on it to obtain more detailed help for that specific screen.
- The **bottom** section labeled "Messages", contains a screen description, instructions and when generated, error messages to assist with accurate data entry.

2.4a MAIN TASKS menu screen for Enter/Edit and Manage Data mode (figure)



The tasks/actions which can be accessed from the TASKS menu screens are:

- Data entry of forms
- Enroll participants (not available for the tutorial)
- Randomization override (enabled only at the DCC)
- Study drugs (only available for a treatment trial)
- Print option for blank forms and participant labels
- Listings or reports
- Authorize PIN (only available in tutorial)
- Exit system

Select a task by clicking on the button for the task. Many of these tasks bring up additional menus. Each of the tasks on these menus is described later in this manual.

Selection of the *Exit* option will take you back to the desktop. To restart the data system from the desktop, double click on the Internet Explorer icon if the NASH CRN data system is your home page, or enter through the NASH CRN website.

3. Tutorial system

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3.1. Introduction

The tutorial system is designed to let you practice data entry for a participant using the forms listed in Appendix 11.2 and to become data entry certified. After completing the tutorial and faxing all requested documentation to the Data Coordinating Center (DCC), you will be certified to enter, edit, and manage your clinic's data using your authorized unique Personnel Identification Number (PIN) and password. Section 3.2 lists all of the steps in the data entry certification process.

Before beginning the tutorial, you must request a PIN from the DCC if you have not already been assigned one, and print the tutorial forms. The tutorial forms are completed with data from an example participant and are ONLY to be used with the tutorial.

To request a PIN from the DCC:

1. Go to the NASH CRN website (http://jhuccs1.us/nash)
2. Click on *Studies*, then *Database 2*, then *Data forms*, then *Administrative forms* from study of interest
3. Print and complete the certification forms, Personnel Certification (PC) and Knowledge Assessment (KA)
4. Fax to the DCC at 410-955-0932
5. The DCC will send you your unique PIN via e-mail.

To print the tutorial forms, either:

- Click on the link given in Appendix 11.2,
- From the NASH CRN website, click on *Studies*, then *Database 2*, then *tutorial forms* under the SOP III link, or
- From the database home page, click on *print tutorial forms* (see figure 2.3a)

NOTE that only one person per clinic may do the tutorial at a time. The tutorial and the PIN authorization must be completed before another person may start the tutorial. The tutorial takes an average of 1.5 hours or less to complete.

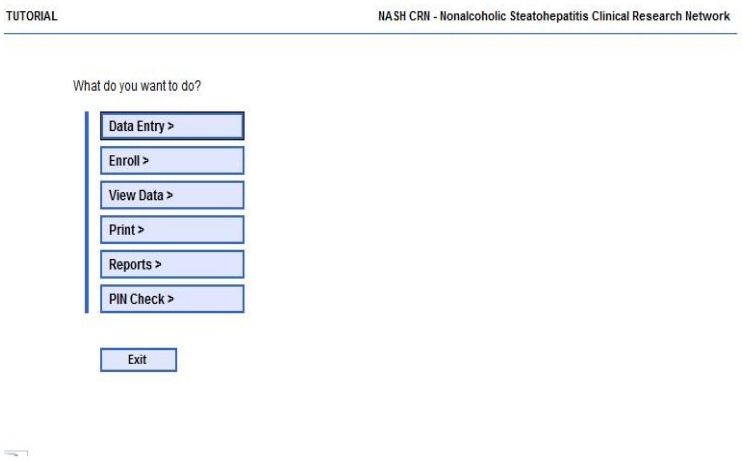
To use the data system tutorial:

1. Make sure that no one else from your clinic is keying forms in the tutorial data system.
2. Access the Data System through the Internet Explorer (see section 2.3).
3. Verify that your Internet browser's POP-UP blocker is set to OFF.
4. Click on *Tutorial and Certification*
5. Log-in to the tutorial using username = **nashdb**, password = **keysmart11**, then click *OK* (see figure 2.3b).
6. Log-in to your clinic's site using your Clinic ID (see Appendix 11.1) and your assigned PIN

7. Key your password. The first time you access this screen you will define your own password. Choose a password with 4 to 8 characters that you will remember and do not share it with anyone. Due to security issues, this password should be unique to each individual; define a **different** password from those used for the NASH CRN data system or NASH CRN website.
8. Click on *Submit*.

The first screen in the tutorial is the tutorial TASKS menu screen (see figure 3.1a) which is similar to the MAIN TASKS menu (figure 2.4a). To data enter forms, browse the data, print labels or tutorial forms, create listings or reports and to run the PIN check, click on the appropriate TASK button. To exit the system and return to the desktop, click on the *Exit* button. The Enroll task is not available in the tutorial.

3.1a Tutorial TASKS menu screen (figure)



3.1. Introduction

Most of the tasks in the actual NASH CRN Data System are available in the tutorial to enable you to practice and become familiar with the capabilities of the data system. This chapter has not been designed to teach you this. Detailed instructions are given in Chapters 4 though 9, and the tutorial directions refer to pertinent sections.

The goal of the tutorial chapter is to inform you of the details of how to become data certified and how to start the data entry process. The data system is very user-friendly, so keying the forms **exactly** as completed and following screen prompts is generally sufficient to complete the tutorial.

Users are highly encouraged to read this manual and explore the various functions, reports and listings available, as a component of the certification process. Also, Appendix 11 includes summary tables of the Data Entry codes and rules and the most frequent Data System Errors and their resolution that can be printed and used as a reference.

The PIN and password that you use for the tutorial will be authorized for data entry and management when you finish the tutorial, run the PIN check, complete the Data Entry Certification/Decertification (DC) form, and fax all requested documentation to the DCC. The PIN allows access to the clinic's data system and is used to identify the data entry technician.

3.2. Summary checklist for Data Entry Certification

Below are the steps that must be completed before the DCC will authorize your PIN and password for use of the data system. After you are certified, you may use the NASH CRN data system to enter and manage data and create reports for your clinic.

NOTE: Only one person per clinic may complete the data system tutorial at a time. Your PIN authorization must be completed before another person may start the tutorial. Plan around 1 hour to complete the tutorial process.

- ☐ 1. Review this manual and the NASH CRN study's protocol.
- ☐ 2. Complete the Personnel Certification (PC) and the Knowledge Assessment (KA) forms and fax to the DCC at 410-955-0932 to request your unique PIN. The DCC will e-mail you your unique PIN. (See section 3.1).
- ☐ 3. Download and print tutorial forms (see Appendix 11.2).
- ☐ 4. Verify that your internet browser's POP-UP blocker is set to OFF (see Section 2.3). Log-in to the NASH CRN tutorial system using your assigned PIN and a 4-8 letter password of your choice.
- ☐ 5. Register the example participant by double data entering the tutorial RG0 form (see Section 3.3).
- ☐ 6. Print a copy of the RG0 form's confirmation screen (see Figure 3.3d).
- ☐ 7. Print the labels for the screening visit b from the *Print* button on the RG0 form confirmation screen (see Section or 3.3).
- ☐ 8. Key the rest of the tutorial forms, print a copy of each form's confirmation screen. (See section 3.4).
- ☐ 9. Practice browsing and changing data and other tasks available in the tutorial (see Sections 3.4 and 3.5).
- ☐ 10. Upon completion of the tutorial, select the *PIN check* option from the tutorial TASKS menu. Resolve any errors, then re-run the PIN check. (See Section 3.6).
- ☐ 11. Print the tutorial authorization screen (see Figure 3.6c).
- ☐ 12. Complete the Data Entry Certification/Decertification (DC) form.

☐ 13. Fax copies of the following to the DCC at 410-955-0932:

- The confirmation screen after data entry of each tutorial form
- The tutorial authorization screen
- The completed DC form
- The screening visit labels generated after registering the example participant

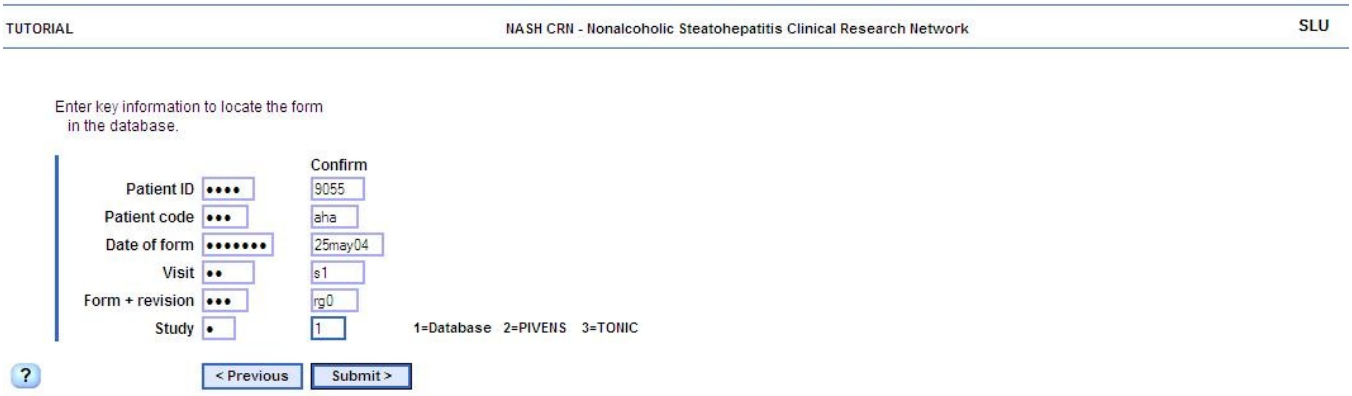
☐ 14. Congratulations! You are certified to use the NASH CRN data management system once you receive the e-mail from the DCC confirming that your PIN is activated for data entry.

3.3. Participant registration

After log-in to the tutorial data system, the next step in the tutorial is to register the example participant by keying the tutorial Registration form (RG0). No other forms can be data entered until the RG form is keyed without errors. Detailed directions for the data entry of a form are given in sections 3.4 and 7.1. An outline of the steps to register the example participant are:

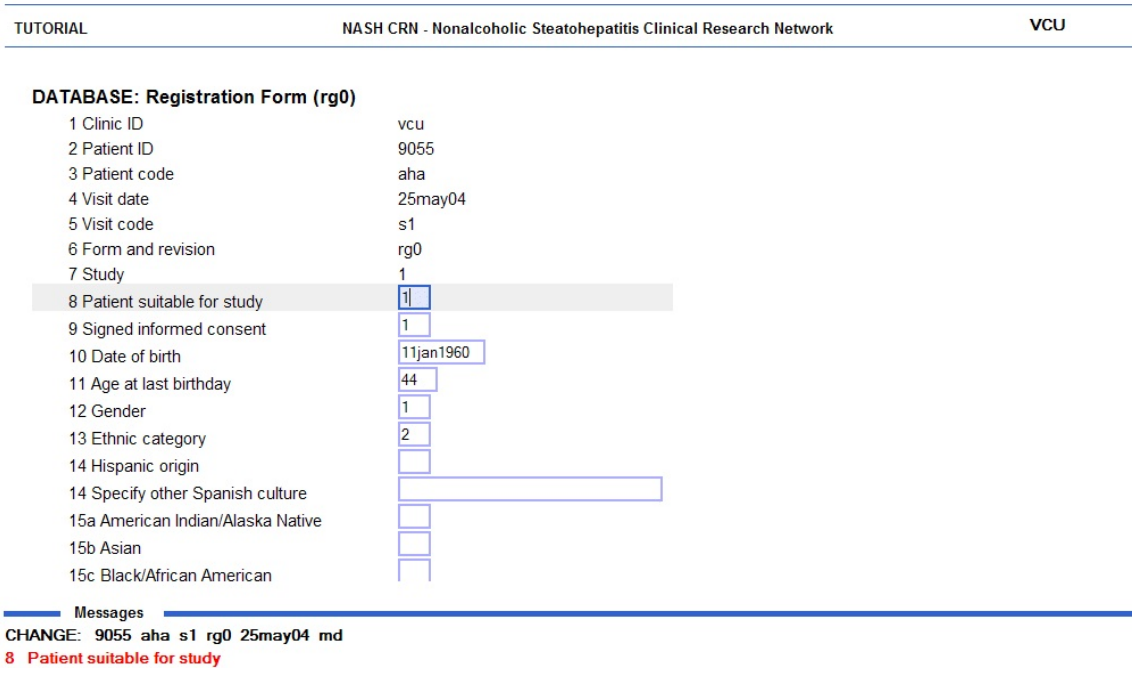
1. Click *Data Entry* on the tutorial TASKS menu (see figure 3.1a).
2. Click *Add a data form* (see figure 3.4a).
3. You do not need to key your clinic ID (item 1 on the form). The data system automatically enters your clinic initials based on the personal log-in data.
4. Key items 2 through 7 (Patient ID = **9055**, Patient code = **aha**, form date = **25may04**, visit code = **s1**, form+revision code = **rg0**, study number = **1**) twice, then click *Submit* (see 3.3a below).

3.3a Tutorial RG0 form (figure)



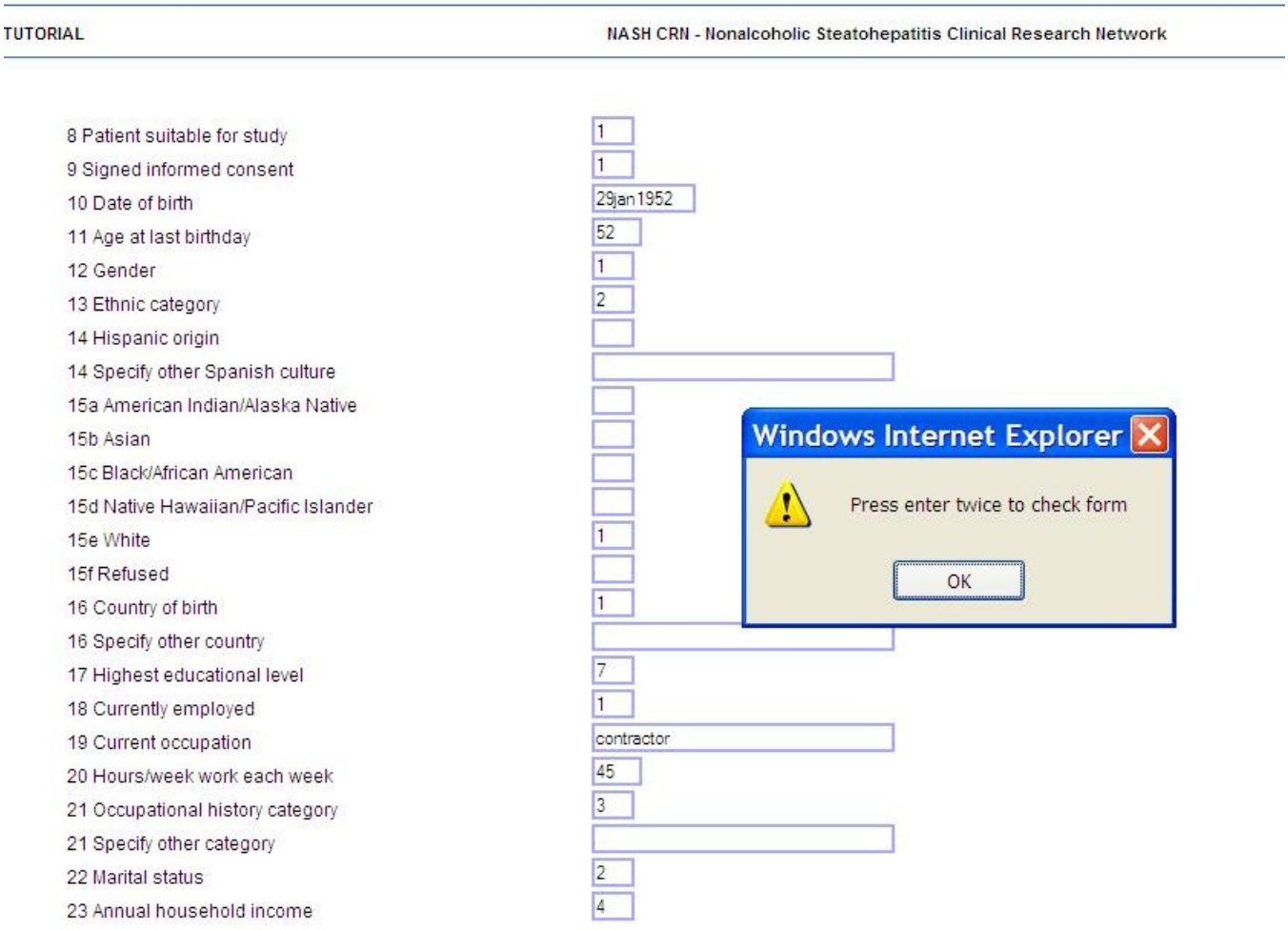
5. The RG0 data entry screen will be in view as in figure 3.3b.
   - Key the response data for the form **EXACTLY** as written on the form.
   - Completely fill all the spaces in the date fields; Date of birth (item '9' in the "ddmmmyyy" format, and other dates in the "ddmmmyy" format)
   - Key a signature as '**1**'

3.3b Tutorial RG data entry screen (figure)



7. Press **ENTER** twice when prompted by the pop-up window which appears after keying the last item of the form (see Figure 3.3c).

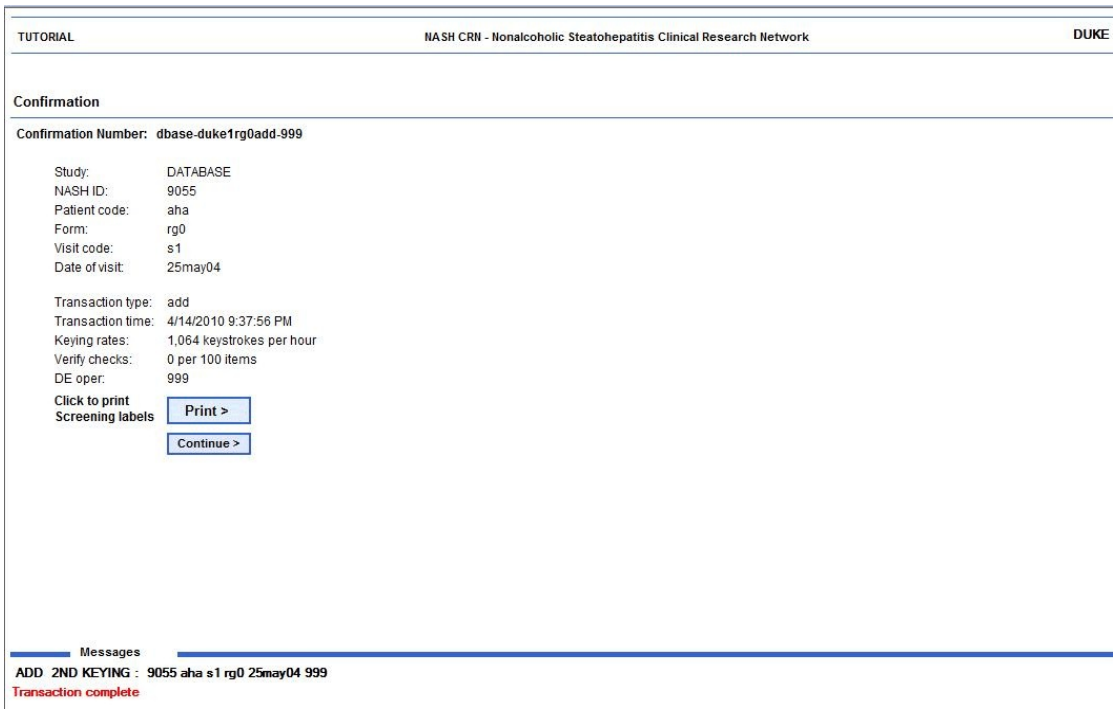
3.3c Form check after first data entry keying (figure)



8. Correct any data entry errors flagged by the error messages and then click *OK* or press **ENTER** once the next pop-up window is in view (see figure 3.4c).
9. Key the form data again, and resolve any error messages.
10. Click *OK* ONCE to save the form data in the final pop-up window (see figure 3.4d).

Once you have keyed the tutorial Registration form, a screen will appear confirming that you have successfully registered the participant. Print a copy of the confirmation screen (see figure 3.3d).

3.3d Confirmation screen for the tutorial RG form (figure)

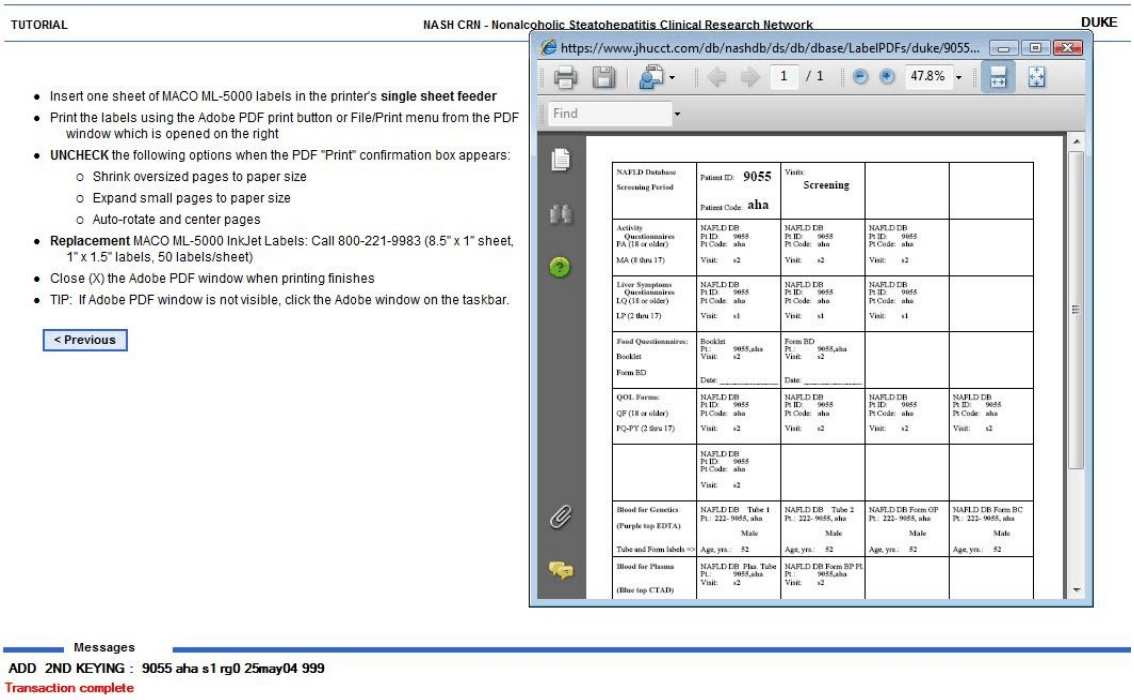


Print the labels for the participant's screening visit by clicking on the *Print* button next to "*Click to print Screening labels*" on the Registration form's confirmation screen. For instructions on which labels to use and printing labels, see section 8.2. Briefly, the steps to print the screening visit labels from the confirmation screen are:

1. **Make sure your internet browser's POP-UP blocker is set to OFF**
2. Click on the *Print* button next to "*Click to print Screening labels*"
3. A screen with the participant's labels appears in a PDF file format (see figure 3.3e).
4. Insert one sheet of labels in the printer's single sheet feeder

5. Print the labels using the Adobe PDF PRINT icon or the PDF File/Print menu
6. **Uncheck** the following options when the PDF "Print" confirmation window appears:
   - Shrink oversized pages to paper size
   - Expand small pages to paper size
   - OR Fit to printer margins instead of above 2 options
   - Auto-rotate and center pages

3.3e Tutorial screening visit labels PDF file (figure)



3.4. Data entry

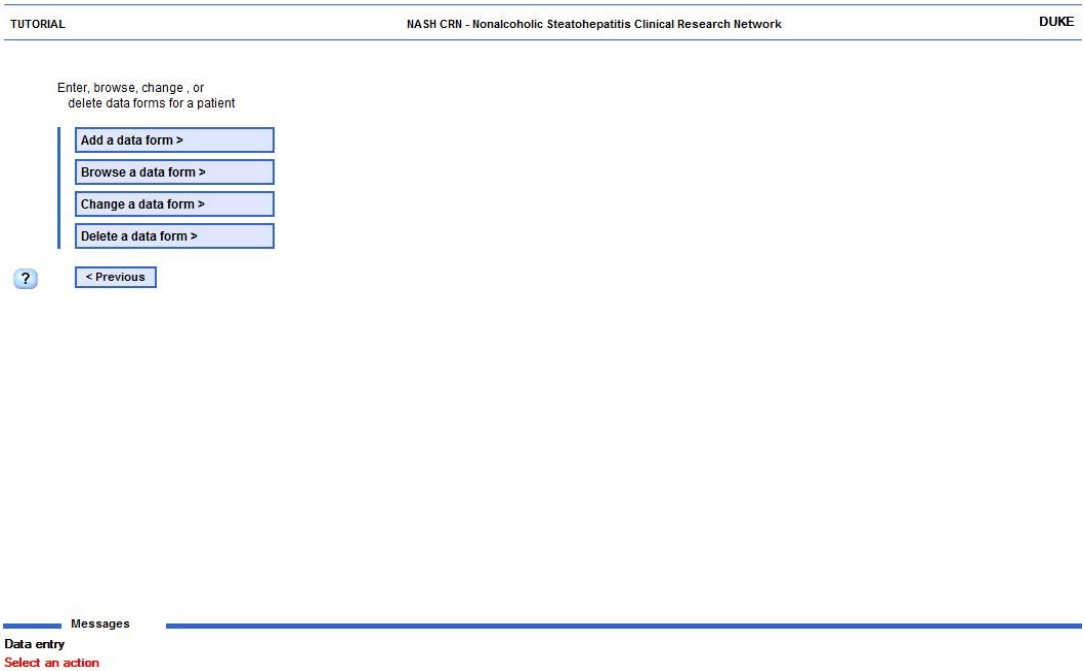
The next step in the tutorial, after keying the registration form (RG), is to key each of the 10 remaining tutorial forms. The process to key each tutorial form is the same as that given in the previous section for the tutorial RG form. A confirmation screen appears after each form is successfully keyed and saved. For the tutorial only, PRINT a copy of each form's confirmation screen which will be faxed to the DCC at the end of the tutorial along with other tutorial materials. When keying data for study participants, it is not necessary to print confirmation screens.

The data system uses **double data entry** which requires that each form's data be entered twice. Though this may seem tedious at first, it is a method that helps to flag many keying and consistency errors BEFORE the data are saved to the electronic database, helping to ensure accurate study data, reducing the number of data audit errors and saving much time in the long run.

NOTE: that data can be saved only for a form keyed twice with no data entry errors. You cannot save your work in the middle of the form.

Click on the *Data entry* task on the tutorial TASKS menu screen (see figure 3.1a). The DATA ENTRY menu screen will appear as in figure 3.4a. The tutorial DATA ENTRY menu is the same as that for the NASH CRN data system (see figure 7.1a).

3.4a DATA ENTRY screen (figure)



There are four data entry actions:

- **Add** - to enter new data forms
- **Browse** - to browse previously entered data forms (i.e., look at but do not change)
- **Change** - to change previously entered form data
- **Delete** - to delete previously entered data forms

Clicking on *Previous* returns the system to the tutorial TASKS menu screen.

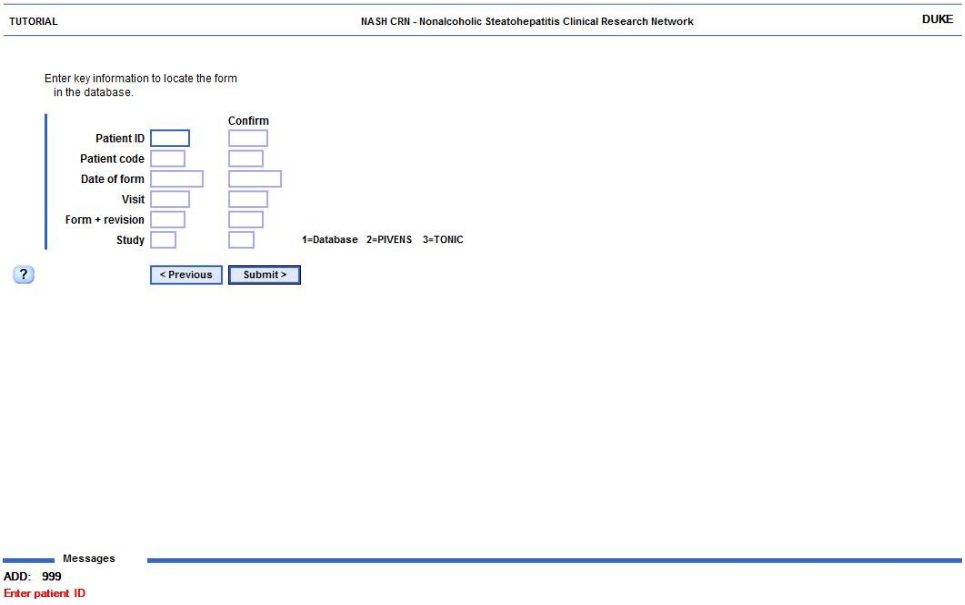
General guidelines for the keyboard during data entry are:

- Set **Num Lock** on, **Caps Lock** off, **Insert** off
- Use numeric keypad to ENTER numeric data
- Press the **ENTER** key after each item is keyed
- Alternatively, use the scroll bar or mouse and click on the field to be keyed
- Press **Shift+Tab** simultaneously or use the mouse to go back to previously keyed items
- Use the mouse to navigate around the screen

The **Add** task will be used most often in this tutorial; however, as forms are keyed, it is a good idea to practice the other data entry actions to browse, change and delete form data. Each data entry task is described in further detail in Chapter 7.

To enter the data for a new form, click *Add a data form* on the tutorial DATA ENTRY menu. Key items 2 to 7 of the form. These items are called "key variables" and are located in Section A of each data collection form (see figure 3.4b). The key variables uniquely identify the form for a participant, visit, and study. Each data item must be keyed twice. After keying this information, hit **ENTER** or click on *Submit*.

3.4b Key variables screen (figure)



For all of the tutorial forms, key the following values for the key variables:

- Patient ID - **9055**
- Patient code - **aha**
- Date of form - date form was completed, which is item 4 on every form
- Visit code - item 5 on every form, either a **S1** or an **S2**
- Form + revision code - the form code and revision number, e.g., **rg0**, **lr0**,..., which is item 6 on every form
- Study number - **1** for the Database study

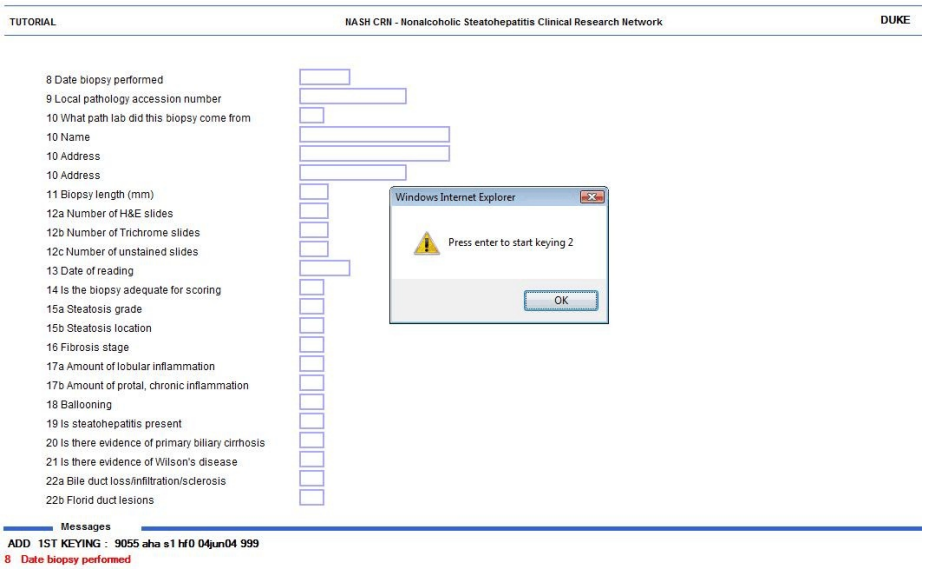
The form's data entry screen will then be in view as shown in figure 3.3b. **ALWAYS key the data exactly as they appear on the form**. Failure to do so is a serious violation of the integrity of the study.

Data entry rules by type of form item are given in Appendix 11.3. Those used most frequently in the tutorial are:

- Completely fill the data entry space except for special response codes (e.g., m=missing), other-specify, or General Comments fields
- Key a **'1'** if a signature is present; key '**?**' if signature is not present
- Key leading and trailing zeroes for numeric responses. **Do NOT key decimal points or commas.**

Once all consistency checks from the first keying are resolved, a pop-up window appears with instructions to press **ENTER** once as in figure 3.4c. The system then saves the responses from the first keying, clears the responses from the data entry screen, and sets the cursor to begin the second keying.

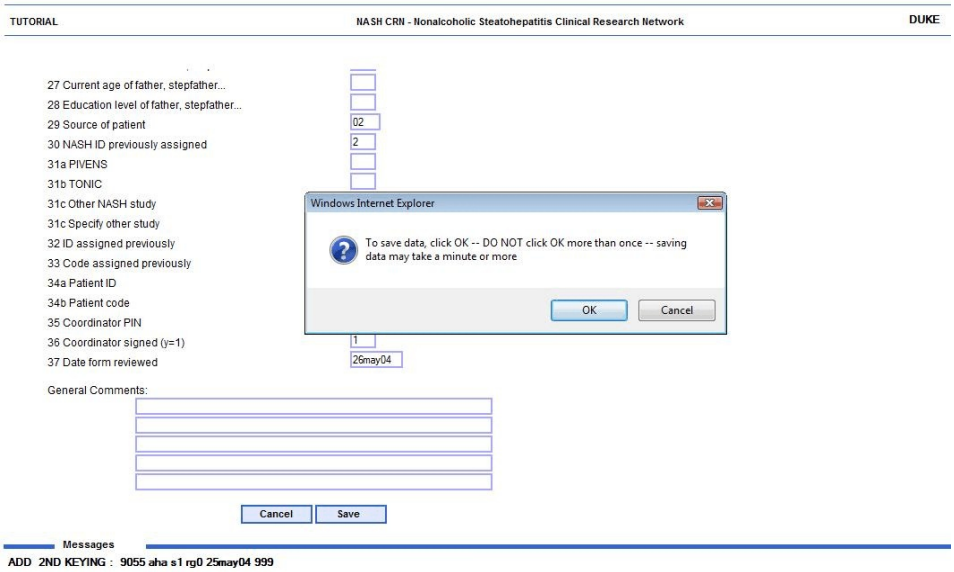
3.4c Clear screen to begin second data entry keying (figure)



After the last item in the second keying is entered, there is a consistency check between the first and second keying. If the second keying of an item does not agree with the first keying, the cursor will move to the item, and an error message containing the value of the first keying will be displayed at the bottom of the screen. The system saves the second keying, so when correcting the second response keyed, make sure that the corrected value is keyed accurately.

Once all data entry errors have been corrected, click the *OK* button ONCE in the pop-up window shown in figure 3.4d to save the data entry values to the electronic database.

3.4d Save the form data (figure)



Remember that the data entry technician should NEVER change the data on the form to what s/he thinks the response should be. If there is a discrepancy that cannot be resolved, the data entry technician should consult with the study coordinator.

Errors in the tutorial data entry can be corrected immediately by the technician. The first step is to compare the keyed and recorded form values to verify that the value is in the correct format, that decimal points are not keyed, leading and trailing zeroes are keyed, and that skip patterns are followed correctly. Appendix 11.6 lists common data entry errors and their resolutions.

KEY OTHER TUTORIAL FORMS OR EXIT DATA ENTRY TASK:

To key another form, select *Data Entry*, then select *Add a new form*, and enter the key fields for the next form to be keyed.

To exit the DATA ENTRY screen and return to the tutorial TASKS menu screen, click on *Previous*, or click on the backward arrow icon on the internet toolbar.

3.5. Additional tutorial TASKS menu functions

Besides the tutorial data entry and PIN check functions described in sections 3.4 and 3.6, respectively, there are additional tasks/functions that can be accessed from the tutorial TASKS menu screen. Though not required for data entry certification, practice using these functions within the tutorial is suggested before managing the clinic's data system. This will familiarize you with the various reports and listings that can be generated through the data system.

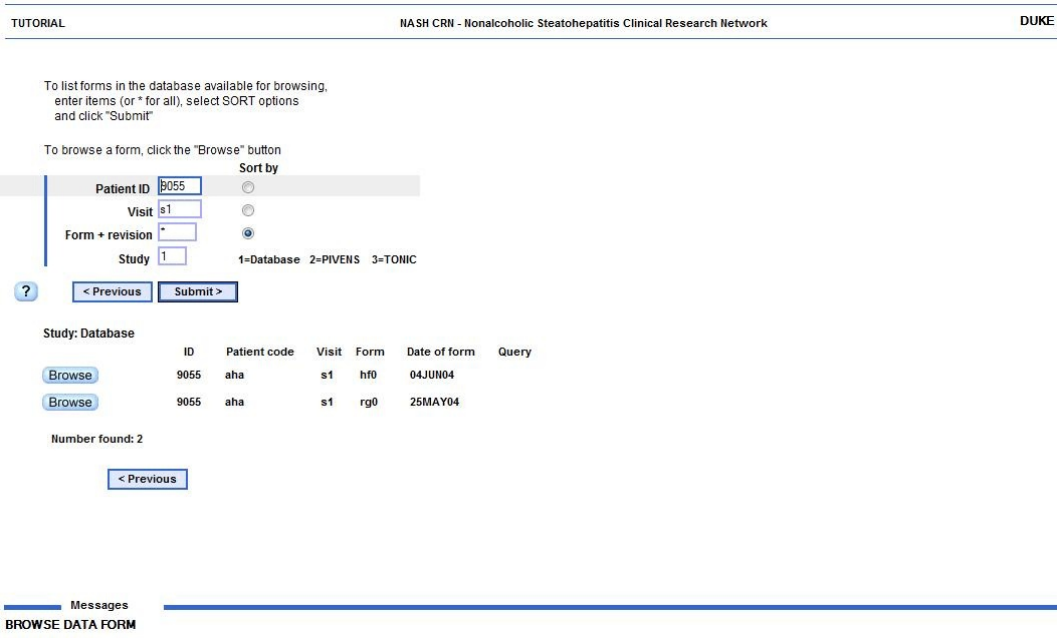
The Enroll task is not available in the tutorial. If the *Enroll* button is clicked, the error message, 'Enroll not available in Tutorial', is returned.

VIEWING DATA:

There are two ways to view data: you can browse data (look at but not edit) or you can change data (edit).

To browse the data, click on the *Data Entry* button on the tutorial TASKS menu, then click *Browse a data form* to display a list of forms entered into the data system (see figure 3.5a). The form list can be sorted by Patient ID, visit code or form + revision code by clicking on the SORT order option button. Keying an asterisk (*****) for ID, visit, and form + revision displays all of the forms entered in the data system for the specified study (key study = **'1'** for the tutorial). Clicking on the *Browse* button next to a specific form will bring up that form.

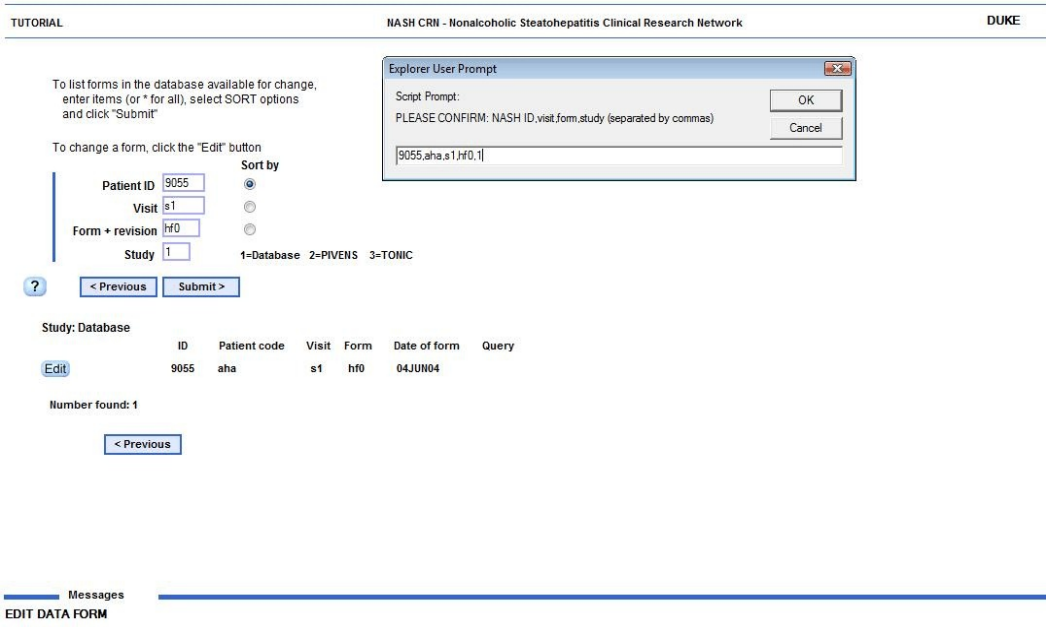
3.5a Tutorial Browse data display (figure)



There are 2 ways to view form data and also be able to make a change to the data. One is to click on the *View Data* button on the tutorial TASKS menu screen and the other is to click on the *Change a data form* button on the DATA ENTRY menu. Both display a list of forms in the data system that can be edited (see the form list in figure 3.5b). The form list can be sorted by Patient ID, visit code, or form + revision by clicking on the SORT order option button. Keying an asterisk (*) for patient ID, visit, and form + revision for a selected study displays all of the forms in the data system. Clicking on the *Edit* button next to a specific form will bring up that form in change mode after verification of ID, visit, form and study.

Click on the *Edit* button to display a selected form in CHANGE mode. First, a dialog box requesting confirmation of the NASH CRN patient ID, visit code, form + revision code, and study number will pop-up, as in figure 3.5b. Type each item requested separated by commas and click *OK*.

3.5b Dialog box for confirmation of data record to be edited (figure)

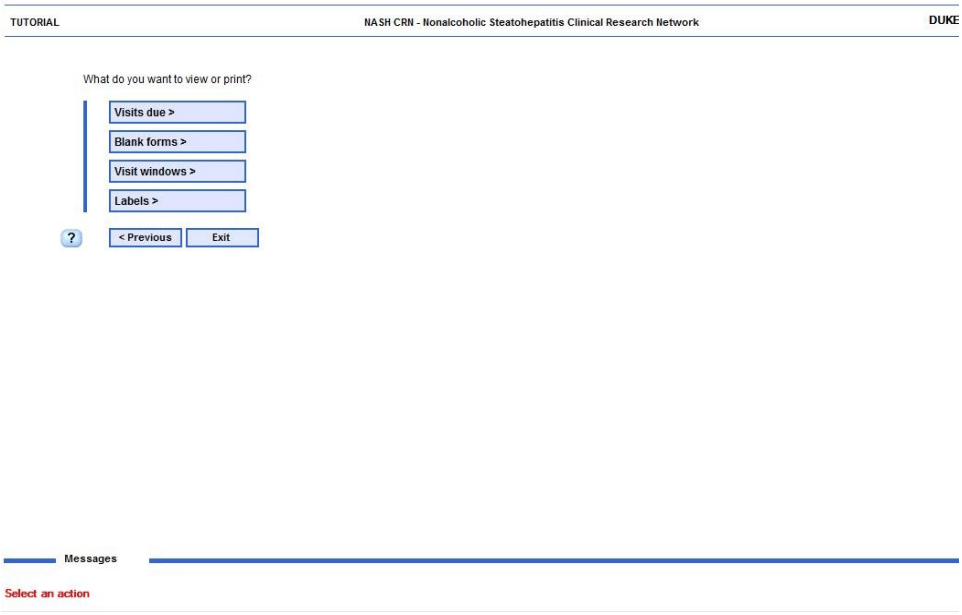


The requested form will be in view and changes can then be made to the data. Press ENTER after making the changes and the data system will perform the checks for data entry errors and inconsistencies.

PRINT TASK:

There are three active print options available from the tutorial print function. Clicking on the *Print* button on the tutorial TASKS menu results in the tutorial PRINT menu screen shown in figure 3.5c. The tutorial **Print Visit windows** option is not enabled. Clicking on the *Previous* button on each print task entry screen returns the system to the tutorial TASKS menu screen.

3.5c Tutorial PRINT menu (figure)



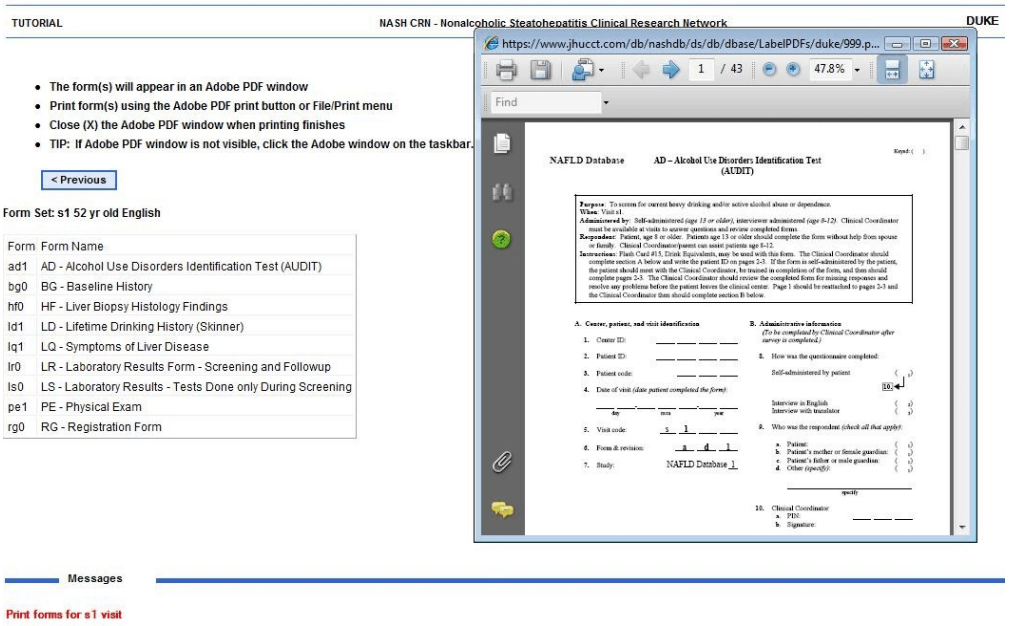
The tutorial **Print Visits Due** option will display a list of participants with a visit target date in a given month. Click on the *Visits due* button on the tutorial PRINT menu, enter the study (**1** for Database), month (as 01-12), and year (4 digits) of the target date. The list can be printed by clicking on the PRINT icon. See section 9.12 for further description.

The tutorial **Print Blank Forms** option will display any tutorial form in a PDF file format that can then be printed using the Adobe PDF PRINT icon or File/Print menu. Either a single form (option 1) or a form set for a specific visit (option 2) for the forms used in the tutorial can be printed.

1. Be sure to set your internet browser's POP-UP blocker to OFF.
2. Click on the *Blank forms* button on the tutorial PRINT menu.
3. Key the print option, form or visit code and study number (key study **1** for the tutorial).
4. Click on *Submit*
5. **NOTE: This option is available in the tutorial only. See section 8.1 for additional information.**

Figure 3.5d displays the output when printing the form set for all tutorial screening visits. The forms are listed in alphabetical order.

3.5d PDF file output for the tutorial screening visit form set (figure)



The tutorial **Print Labels** option will display a sheet of labels as a PDF file for any NAFLD Database 2 labels that are needed for data collection forms and whole blood collection tubes for a specified follow-up visit. This file can then be printed using the Adobe PRINT icon or File/Print menu. There is one set of labels per participant visit.

1. Be sure to set your internet browser's POP-UP blocker to OFF.
2. Click on the *Labels*, button on the tutorial PRINT menu.
3. Key the patient ID, patient code, visit code, and study number (key study=**1** for the tutorial).
4. Click on *Submit*.
5. See figure 3.3e for an example of the PDF label file for the Database screening visits.
6. See section 8.2 for detailed instructions on printing visit labels.

REPORTS or LISTINGS:

There are 3 report options available from the tutorial report task. Clicking on the *Reports* button on the tutorial TASKS menu results in the tutorial REPORTS menu screen shown in figure 3.5e. Clicking on the *Previous* button on each report option's screen returns the system to the tutorial TASKS menu screen. A report can be printed using the PRINTER icon.

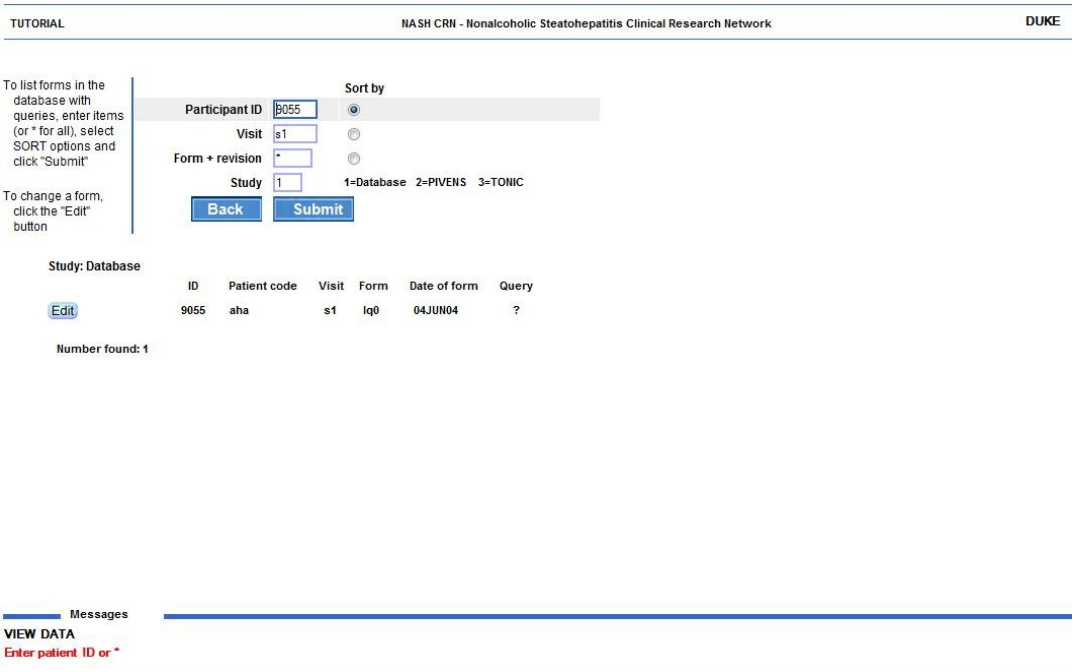
3.5e Tutorial REPORTS menu (figure)

These 3 reports are only a small subset of the 18 automated report listings available through the NASH CRN data system. These are very useful in managing your clinic's data, aiding in report creation, determining which patient visits are due, and which data items are still not complete. Section 9 provides detailed directions and screen views for each of the 18 available reports.

The tutorial **Queries** report displays a list of forms with unresolved queries, which are data records containing a question mark (**?**), which is a special edit code, for the tutorial participant. If a **?** was entered for any item on a form, the form is considered incomplete; the **?** signifies that the information is temporarily missing. These items must be resolved as data become available.

1. Click on the *Queries* button in the tutorial REPORTS menu.
2. Key the Patient ID = **9055**, visit code = **S1**, form + revision code, and study number = **1**.
3. Click *Submit*.
4. To list all forms with outstanding queries (**?**) in the data system, key an asterisk (*) for each item except study number (see figure 3.5f).
5. By clicking on the Edit button, the form data will be viewed in CHANGE mode.
6. Section 9.7 gives directions for the similar data system report listing.
7. Appendices 11.3 and 11.5 give additional information about the use of the special query code.

3.5f Tutorial Queries report (figure)

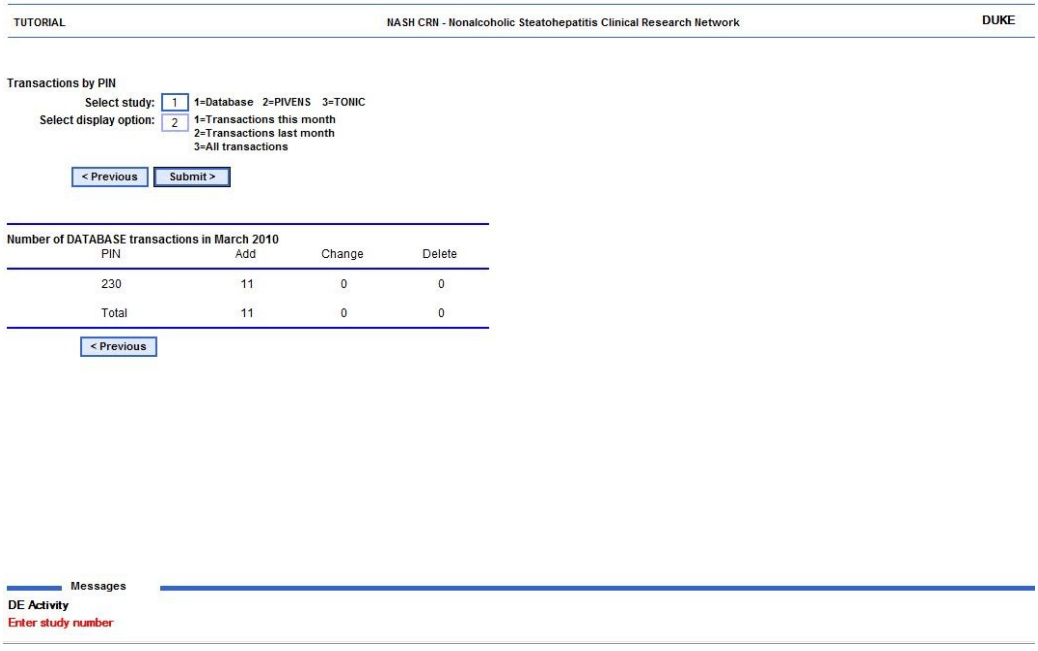


The tutorial **Transactions** report option displays a summary table of data entry activities for the tutorial participant's forms by the PIN code of the data user who keyed the form for either the current or previous month or the entire study period (see figure 3.5g below).

1. Click on the *Transactions* button on the tutorial REPORT menu.
2. Key the study number (**1** for Database).
3. Key the activity window option (**1**=this month, **2**=last month, **3**=all).
4. Click on *Submit*.

A report is displayed showing the number of data entry transactions by ADD, CHANGE and DELETE mode for each PIN, and a total number of transactions. See section 9.8 for more details on this report for the NASH CRN data system.

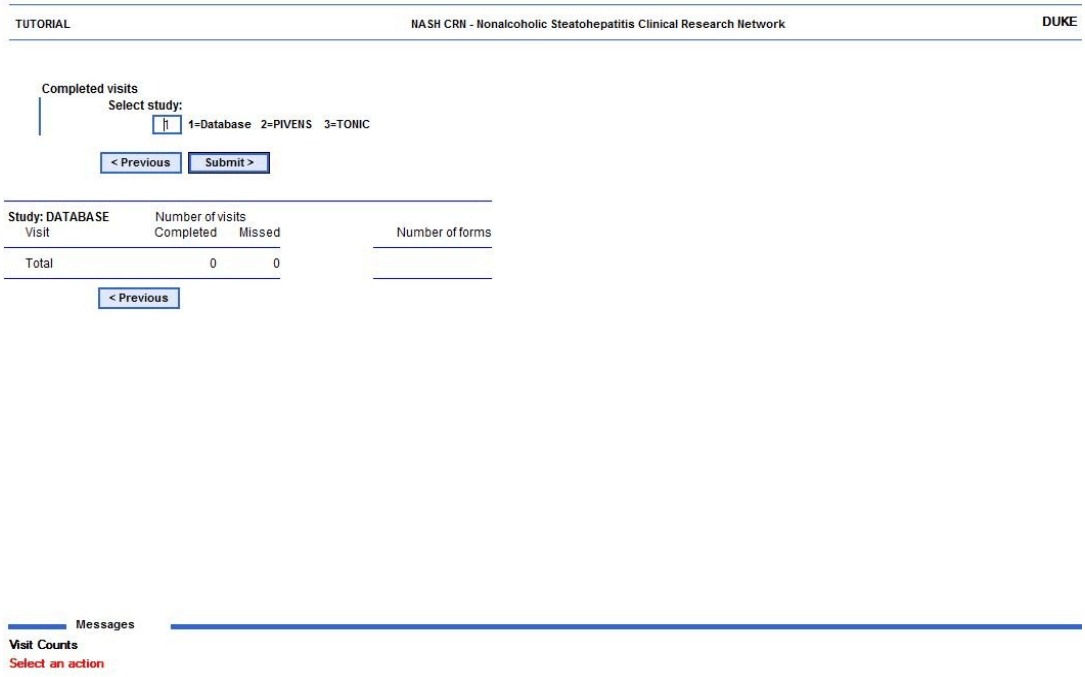
3.5g Tutorial Data Entry Transactions report (figure)



The tutorial **Visits Done** report option displays a table of the number of visits completed, visits missed, and the number of forms keyed by visit code (see section 3.5h below).

1. Click on the *Visits done* button on the tutorial REPORT menu.
2. Key the study number (**1** for Database).
3. Click on *Submit*.
4. Section 9.11 gives detailed information for this report for the NASH CRN system.

3.5h Tutorial Visits Done (figure)

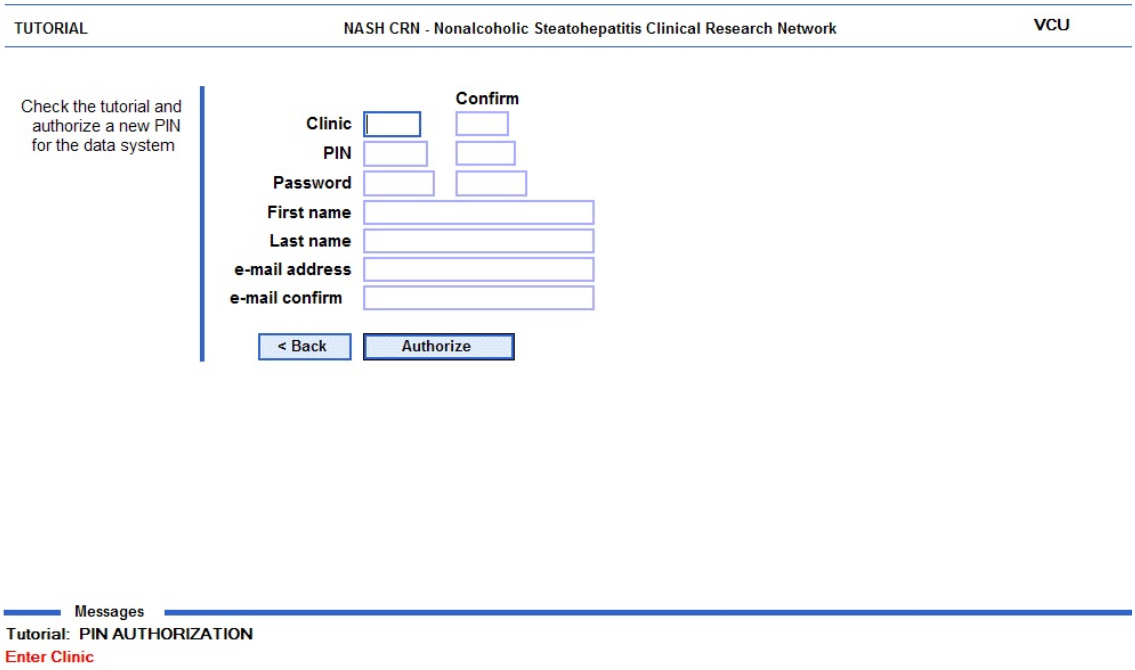


3.6. PIN authorization

Once you have keyed all six tutorial forms, authorization of your PIN and password is the next step in becoming data entry certified

1. Click on *PIN Check* on the tutorial TASKS menu screen.
2. The PIN authorization page is displayed as in figure 3.6a.
3. Double data enter your Clinic ID (lowercase), PIN, password, name and e-mail address.
4. Click on *Authorize*.

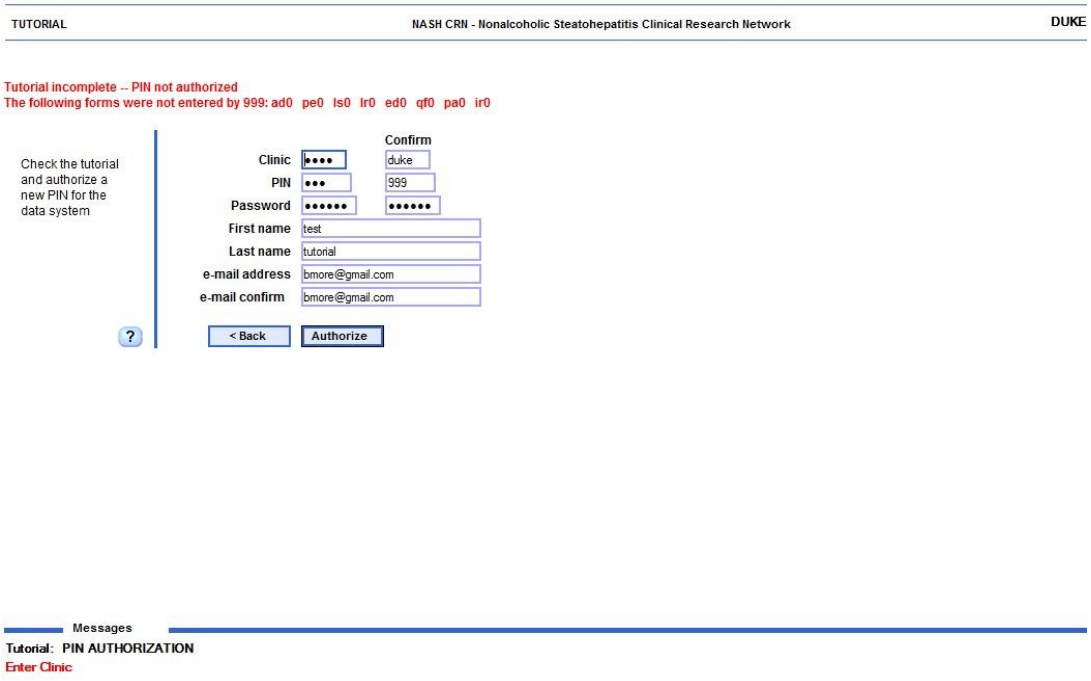
3.6a PIN authorization screen (figure)



The tutorial will be checked for completeness by the data system.

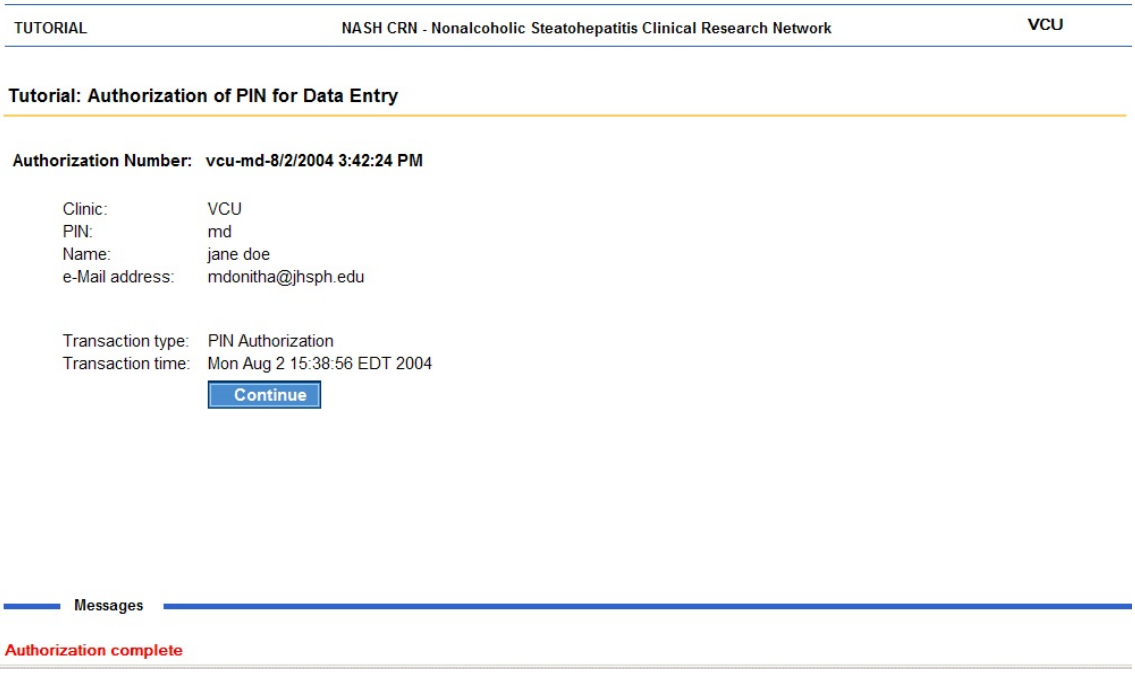
If the tutorial is incomplete, error messages will be displayed as in figure 3.6b. All errors must be resolved, and the PIN check option re-run until there are no error messages.

3.6b Tutorial incomplete (figure)



Once all the checks are passed, an e-mail will be sent to you and to the DCC containing your PIN and password, and the system will display the Tutorial Authorization screen (see figure 3.6c). **Print** the Tutorial Authorization screen.

3.6c Tutorial authorization screen (figure)



Go to the NASH CRN website, click on *Studies*, then the study for which you are being certified, then *Data Forms*, then *Administrative forms*. Print and complete the Data Entry Certification/Decertification (DC) form.

Fax copies of the following to the DCC at 410-955-0932:

- The confirmation screen after data entry of each tutorial form
- The tutorial authorization screen
- The completed DC form
- The screening visit labels generated after registering the example participant.

After review of your materials and forms, the DCC will activate your PIN and password for data entry. You will receive an e-mail confirming that your PIN is activated for data entry.

4. Participant screening and registration

4.1. Registration of participants. 42
4.2. Screening visit labels. 45

4.1. Registration of participants

Before any data may be recorded or keyed for a participant, the participant must give HIPAA authorization and consent to screening for the NASH CRN study or trial. The next step is to print the forms needed to register and screen the patient.

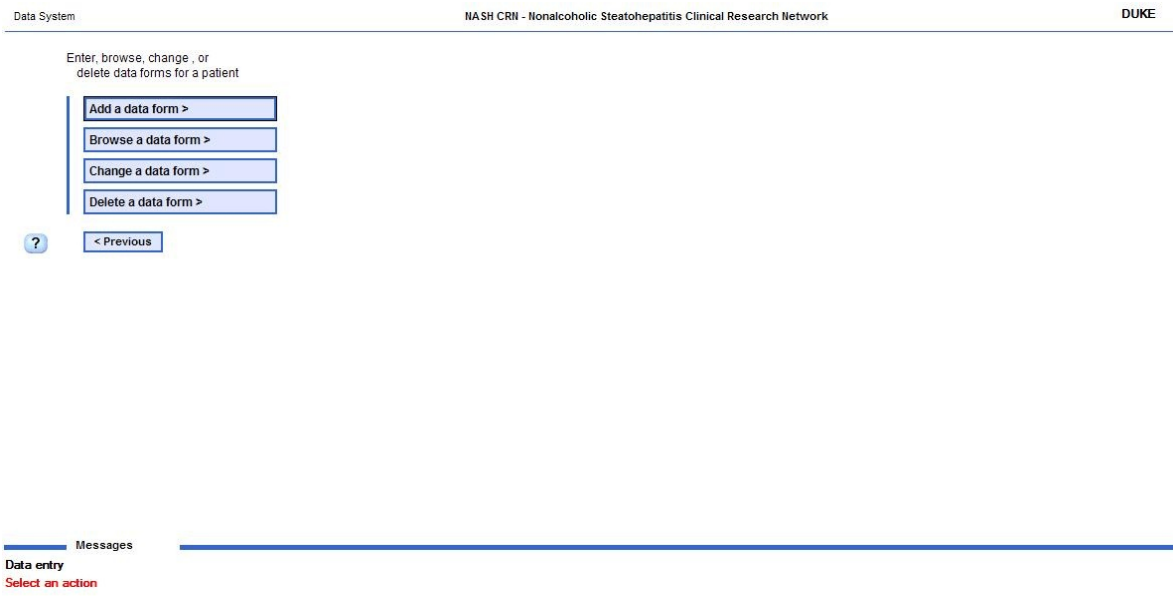
- The form set should be printed from the NASH CRN website by clicking on *Studies* from the left hand menu, the selected study link (Database 2, FLINT, or CyNCh), *Data forms*, and then *Print blank form sets and flash cards*. Then choose the *Baseline visit* form set and flashcards. Instructions to print a form set for a visit are also given in section 8.1.

The participant is registered in the data system by completing and keying the Registration (RG) form. Registration establishes the participant's study identifiers (patient ID number and patient code) in the electronic database.

To data enter the RG form for a participant:

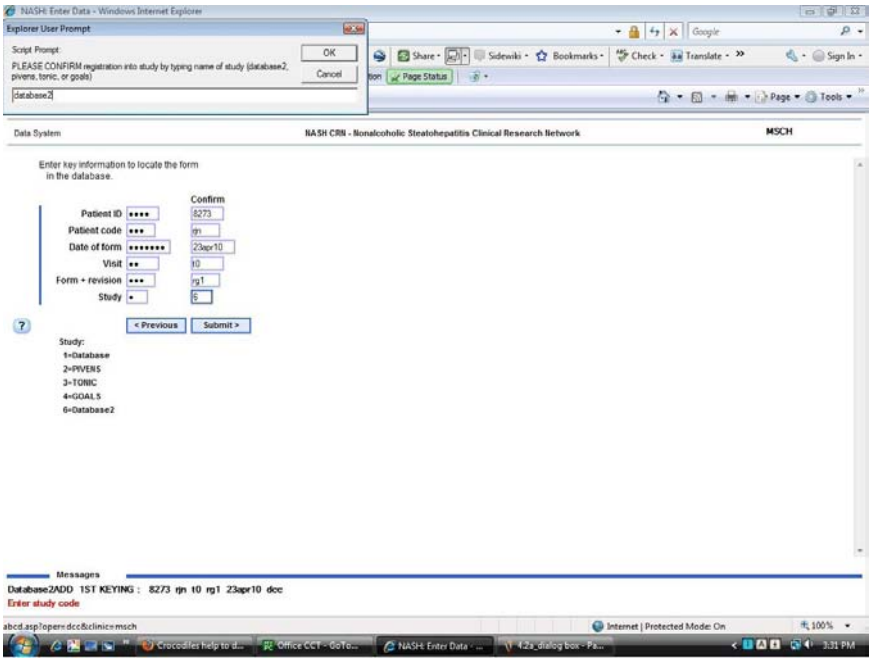
- Ensure that your Internet Explorer browser POP-UP blocker is turned OFF
- Log-in to the NASH CRN data system (see section 2.3)
- Click *Enter/Edit & Manage Data*
- Click *Data Entry* on the MAIN TASKS menu (see figure 2.4a)
- Click *Add a data form* (see figures 4.1a and 7.1a)

4.1a Add a data form (figure)



- Key the RG form items 2-7
- Type the study name (e.g., database2, FLINT, or CyNCh), (see figure 4.1b) in the POP-UP window requesting confirmation of the study after the key variable items (items 2 through 7) are keyed.

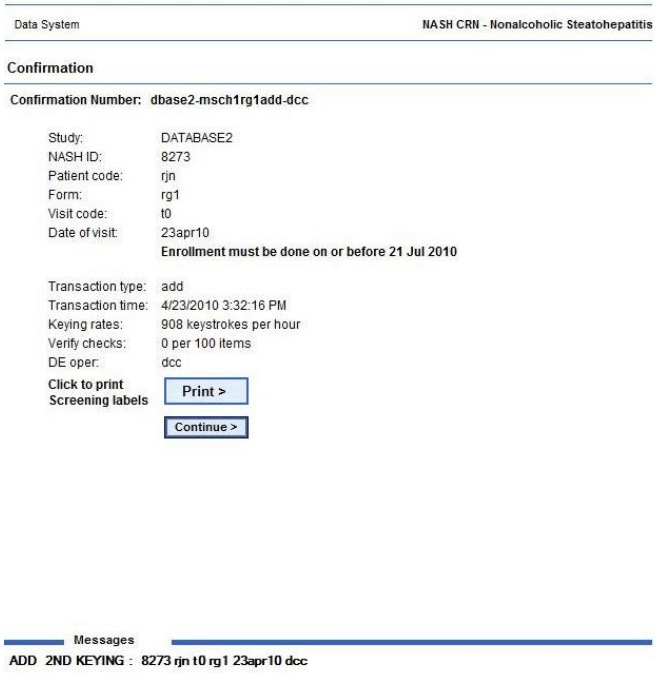
4.1b Dialog box to verify study for the RG form (figure)



- Key the remaining RG form items for the participant exactly as they are coded.

The data system requires that the responses be keyed twice and pass all edit checks before the form data will become part of the database. After saving the form data, a confirmation screen will be in view as in figure 4.1c. The date by which enrollment must be completed is given. Screening visit labels can be printed by clicking on the *Print* button. Detailed directions for the data entry of forms are given in chapter 7.

4.1c Confirmation screen (figure)



Please note that you cannot change the participant's ID number, patient code, or registration date after the RG form is entered, nor can you delete an RG form, so verify that the information is correctly entered before saving the form. If an error is made when completing or keying any of these items, please contact the DCC.

4.2. Screening visit labels

Once you have keyed the Registration form without errors and saved the data by clicking on the *OK* button, a screen will appear confirming that you have successfully registered the participant (see figure 4.1c). Be sure to first set your internet browser's POP-UP blocker to OFF. From this confirmation screen, print the labels for the participant 's screening visit by clicking on the *Print* button next to "*Click to print Screening labels*." A screen with the participant's labels appears in a PDF file format (see figure 4.2a) which can then be printed using the Adobe PDF Printer icon or the PDF File/Print menu. For detailed instructions on printing labels, see section 8.2.

4.2a Screening visit labels PDF file (figure)

FLINT **S Visit**	Patient ID: **4290** Patient Code: **obj**	Visit: **S**		
QOL Forms: QF	FLINT Pt ID: **4290** Pt Code: **obj** Visit: **S**	FLINT Pt ID: **4290** Pt Code: **obj** Visit: **S**	FLINT Pt ID: **4290** Pt Code: **obj** Visit: **S**	FLINT Pt ID: **4290** Pt Code: **obj** Visit: **S**
	FLINT Pt ID: **4290** Pt Code: **obj** Visit: **S**	FLINT Pt ID: **4290** Pt Code: **obj** Visit: **S**		
Blood for Genetics **(Purple top EDTA)** Tube and Form labels =>	FLINT Tube **1** Pt.: **223- 4290, obj** **Female** Age, yrs.: **78**	FLINT Tube **2** Pt.: **223- 4290, obj** **Female** Age, yrs.: **78**	FLINT Form GP Pt.: **223- 4290, obj** **Female** Age, yrs.: **78**	FLINT Form CG Pt.: **223- 4290, obj** **Female** Age, yrs.: **78**
Blood for Plasma **(Green top heparin)** Tube and Form labels =>	FLINT Plas. Tube Pt.: **4290,obj** Visit: **S** Date: _____	FLINT Form BP Pl. Pt.: **4290,obj** Visit: **S** Date: _____		
Blood for Serum **(Red top SST)** Tube Labels ==>	FLINT Serum **1** Pt.: **4290,obj** Visit: **S** Tube Date: _____	FLINT Serum **2** Pt.: **4290,obj** Visit: **S** Tube Date: _____		

4.2. Screening visit labels

Screening visit labels can also be printed at a later time by using the Print Blank Labels task and keying print option = **2** for a form set, visit = **t0** for a Database 2 or s for a FLINT or CyNCh screening visit and the study code (**6** for Database 2, **7** for FLINT, **8** for CyNCh). This is described in detail in section 8.2.

5. Eligibility checking and participant enrollment

5.1. Introduction. 48
5.2. Eligibility checking. 49
5.3. Patient enrollment in Database 2. 52
5.4. Patient randomization (FLINT, CyNCh). 54
5.5. Authorized override of ineligibility. 55

5.1. Introduction

A goal of every NASH CRN study or trial is to enroll (Database 2) or randomize (FLINT, CyNCh) eligible patients with complete baseline data. Each study has its own Eligibility task which checks on completeness of baseline data collection, on time window requirements for data values, and on consistency with the study's eligibility criteria.

Note that the permissible time window checks for various screening tests and/or results are determined in the Eligibility task from the time of the test or data collection either to the registration date or by counting backwards from the current date, which is assumed to be the enrollment date, depending on the protocol requirements.

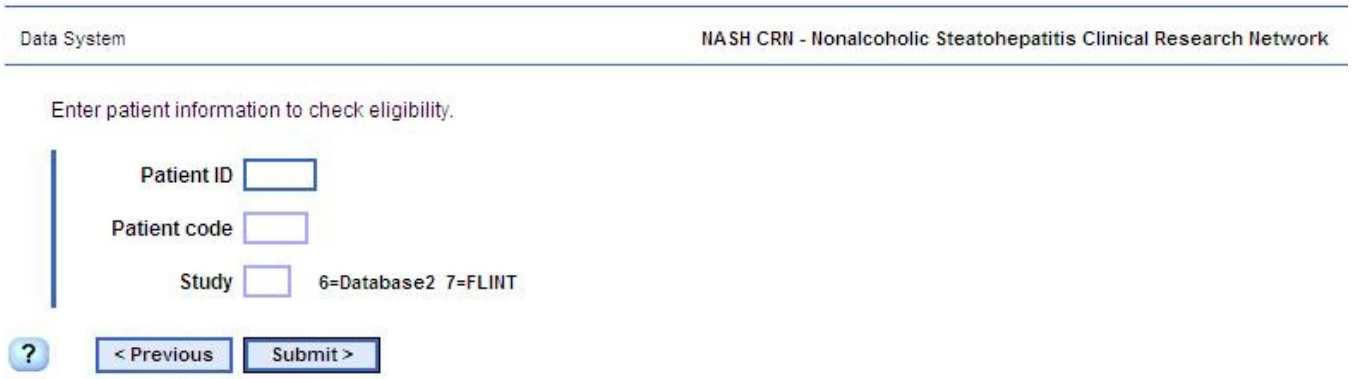
5.2. Eligibility checking

Eligibility checking must be completed successfully prior to enrollment into a NASH CRN study (e.g., Database 2) or randomization into a trial (FLINT, CyNCh). The Eligibility task is the first step in the Enrollment task on the MAIN TASKS menu. Enrollment can only occur if all eligibility checks have been passed.

To check eligibility for a participant:

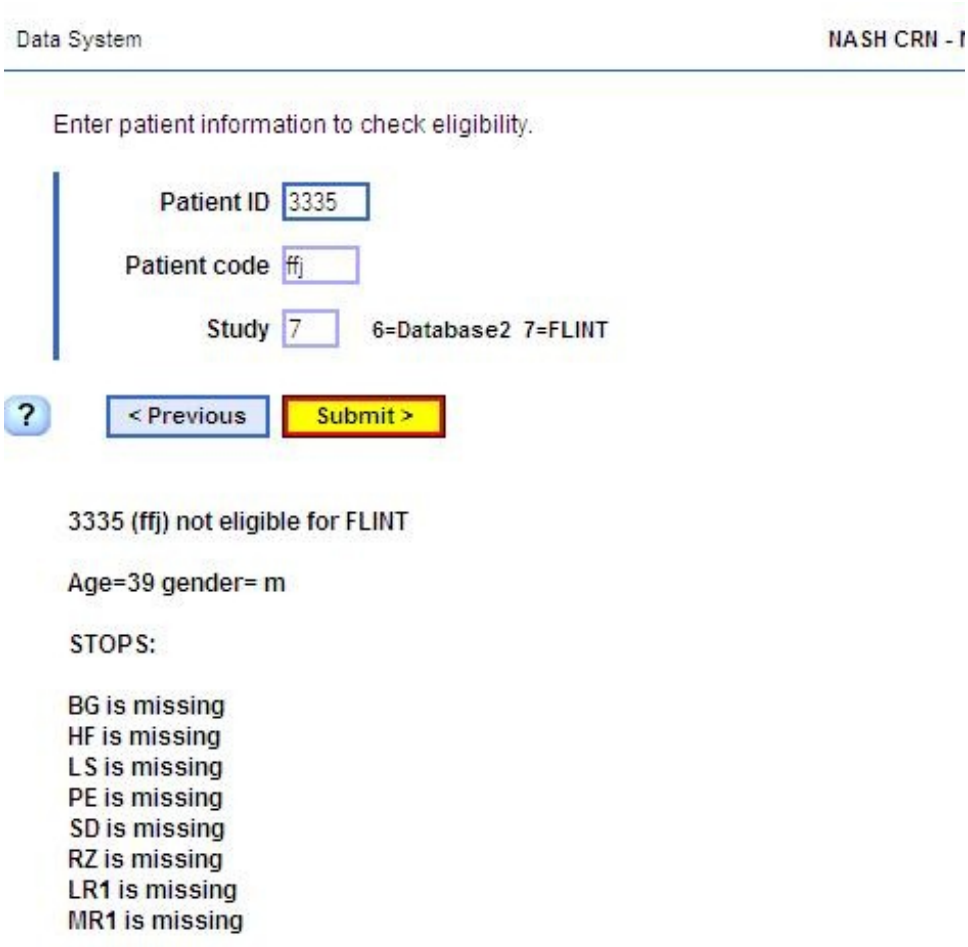
1. Select *Enroll* from the MAIN TASKS menu
2. Key that participant's ID number, patient code and study number (see figure 5.2a)
3. Click on *Submit* to continue.

5.2a Eligibility prompt screen (figure)



If a patient is **not eligible**, then a screen will appear with all Eligibility STOPs for that participant listed as in figure 5.2b.

5.2b Eligibility STOPs (figure)



If the reason(s) for ineligibility can be resolved, such as a screening test that was outside the allowed time window can be rescheduled, then proceed to resolve the listed problems.

If the reason(s) for ineligibility cannot be resolved, such as the participant was found to have a malignancy after their liver biopsy, then inform the patient of their status. Complete and key the Database 2 Enrollment (EN) or FLINT or CyNCh Randomization Checks (RZ) form. This will provide the list of reasons why this participant was ineligible and will no longer be in active screening.

5.2. Eligibility checking

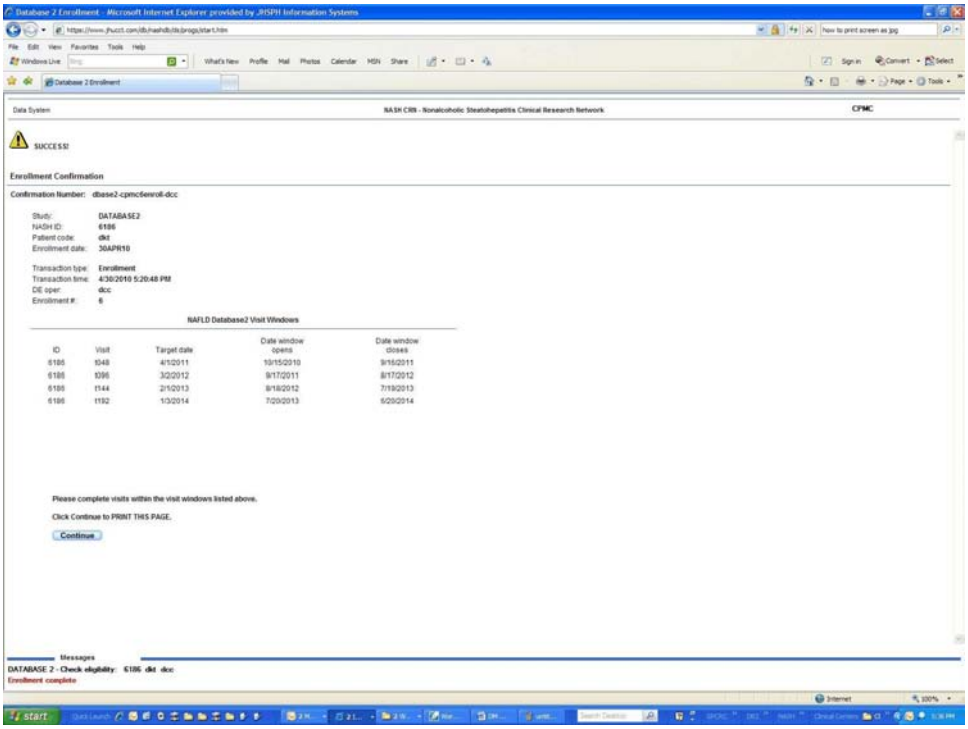
The Eligibility task must be re-run until there are no eligibility STOPs remaining and an enrollment confirmation screen appears. In FLINT and CyNCh an additional screen will ask if you want to Randomize now if the patient is eligible. If it is not clear why there are STOPs, please contact the DCC for help in resolving the problem.

5.3. Patient enrollment in Database 2

A participant may be enrolled into the Adult or Pediatric NAFLD Database 2 study once all eligibility STOPs have been resolved and an enrollment confirmation screen appears in the window. To enroll a participant:

1. On the day of enrollment, confirm that the participant still consents to study enrollment
2. Complete and key the Enrollment (EN) form (use visit code = **t0**)
3. Select *Enroll* from the MAIN TASKS menu
4. Key the ID number, patient code and study number of the participant
5. Click *Submit*
6. If the participant is eligible, the enrollment confirmation screen will be in view (see figure 5.3a). Click *Continue* at the bottom of the screen to print the visit time window listing.

5.3a Enrollment confirmation screen (figure)



If the patient is not enrolled at this time due to unresolved eligibility STOPs, keep in mind that a screening window for a test or procedure may close. The permissible time window checks are determined in the Eligibility task from the time of test or data collection either to the registration date

or by counting backwards from the date the task is run. Therefore, by enrolling the participant on a future date, the time window may close.

The visit time windows listing may also be printed at a later time from the *Listings* task on the MAIN TASKS menu by clicking the *Visit windows* button (see section 9.13).

Labels for use at follow-up visits may be printed at any time from the *Print* task on the MAIN TASKS menu by selecting the *Labels* option (see section 8.2).

The set of forms for each follow-up visit should be printed from the NASH CRN website: jhuccs1.us/nash/closed/cdbase/DB2/dataforms.htm (see section 8.1). The DCC suggests that you not print these forms far in advance of the follow-up visit date, due to possible form revisions that may occur in the interim.

An e-mail will be sent to the DCC and other NASH CRN investigators when a participant has been enrolled.

5.4. Patient randomization (FLINT, CyNCh)

The FLINT/CyNCh enrollment program is used to randomize an eligible patient in FLINT/ CyNCh. Randomization does not happen unless all checks have been passed and the enrollment task has been run. Note that the time window checks for randomization are determined by counting backward from the current date.

To randomize a patient, select Enroll from the MAIN MENU. Enter the ID number, patient code, and study of the patient you wish to randomize. Press **SUBMIT** to continue.

If you press SUBMIT and the patient is eligible, a prompt will ask if you wish to randomize the patient now. If not eligible, the eligibility STOPs will be displayed. To randomize the patient, enter "1" (1=yes) in box next to question, "Randomize now?" **A randomization confirmation will appear that includes the assigned study drug bottles that are to be given to the patient. The confirmation also includes the visit windows schedule for the patient.** When a patient is randomized in CyNCh instructions for drug dosage will also be included in the randomization materials. You will be asked if you want to print the enrollment materials now.

An email will be sent to the DCC and the study investigators when a patient has been randomized.

5.5. Authorized override of ineligibility

This feature is enabled only at the DCC.

If you know the participant will not pass all of the eligibility checks, there is an option to override the checks. Contact the DCC in writing, with an explanation of the problem and a justification for the override. The DCC will review the request and if approved, will complete the randomization override at the DCC when you are ready to enroll the participant. You will need to be in contact with the DCC **prior** to the date you want to enroll the participant, and additional information (e.g., copies of forms and reports) may need to be provided to the DCC.

6. Study drugs

6.1. Dispense study drug. 57
6.2. Drug Inventory. 59

6.1. Dispense study drug

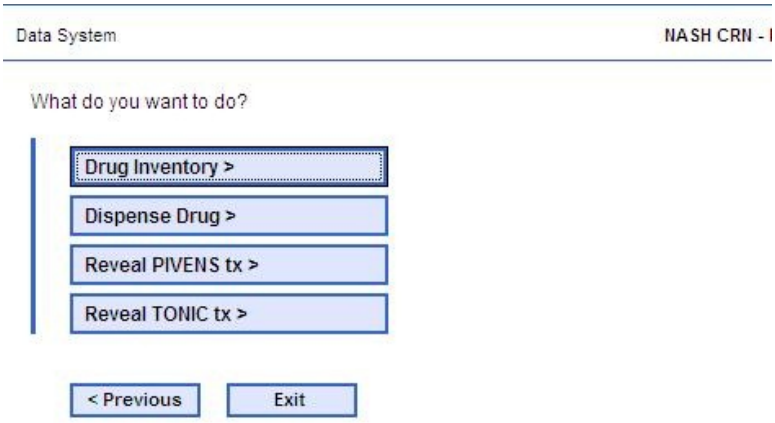
For FLINT:

After a patient is randomized in FLINT, you will need to run the "Dispense drug" task (see figure 6.1a) at or prior to followup visits f12, f24, f36, f48 and f60 to receive the patient and visit specific study drug bottle numbers. To run the task, click on "*Dispense Drug*" from the Study Drugs menu (see figure 6.1a). Enter the patient ID, patient code, the visit date, visit, and study (FLINT= 7) (see figure 6.1b). The data system will print a confirmation of *FLINT* study drug dispensing, which includes the bottle numbers of the study drugs to be given to the patient.

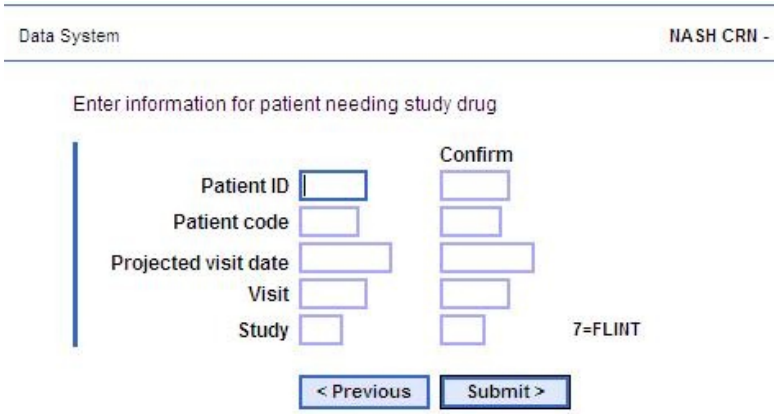
For CyNCh:

After a patient is randomized in CyNCh, you will need to run the "Dispense drug" task (see figure 6.1a) at or prior to followup visits f04, f12, f24, f36 to receive the patient and visit specific study drug bottle numbers. To run the task, click on "*Dispense Drug*" from the Study Drugs menu (see figure 6.1a). Enter the patient ID, patient code, the visit date, visit, and study (CyNCH=8) (see figure 6.1b). The data system will print a confirmation of *CyNCh* study drug dispensing, which includes the bottle numbers of the study drugs to be given to the patient.

6.1a Study drug menu screen (figure)



6.1b Dispense drug screen (figure)

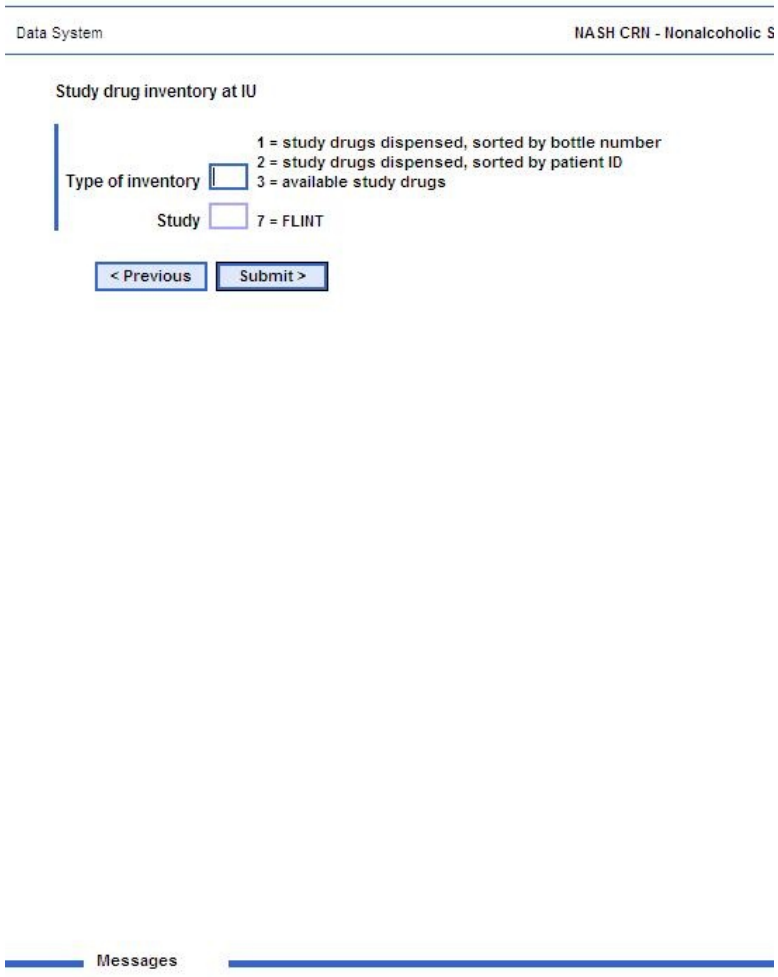


After receiving the study drug bottles from the pharmacy, one tear-off portion of the bottle labels should be put on the Study Drug Dispensing and Return (RD form). For FLINT, the labels should be attached to items 12-13; in CyNCh, the labels go in items 12-22. The RD form should be keyed as soon as possible after the study drugs are dispensed. If any incorrect bottles were dispensed, the data system will not allow the form to be keyed. If incorrect study drugs were dispensed to a patient, contact the DCC as soon as possible.

6.2. Drug Inventory

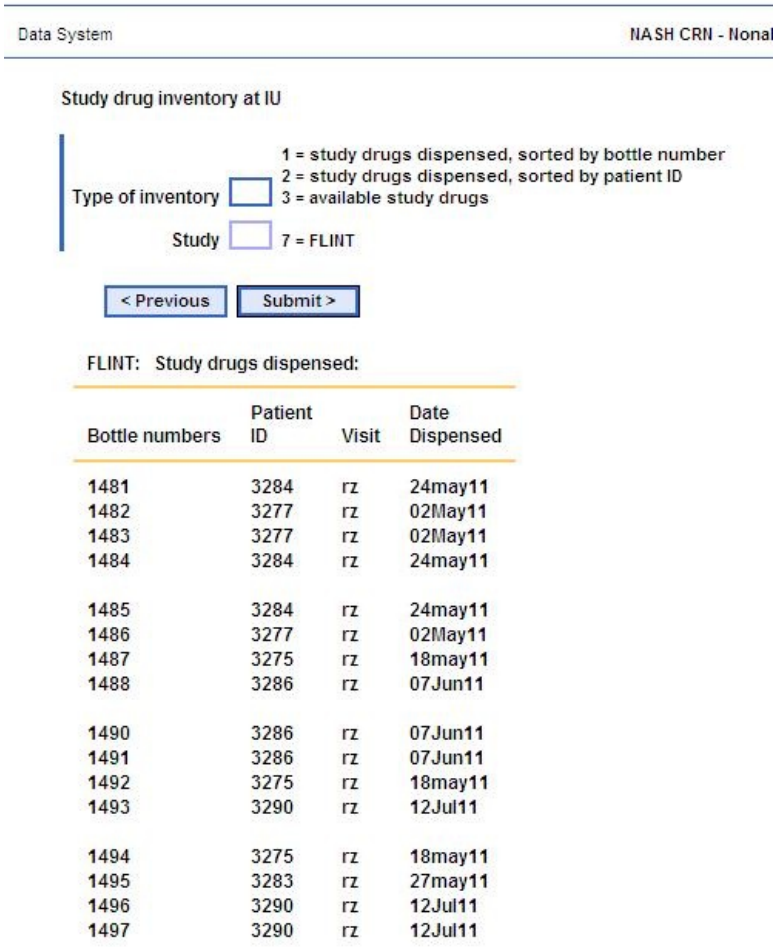
In addition to dispensing study drug, the *Study Drugs* menu also has an option to display the drug inventory. To view bottle numbers that were dispensed to a patient or what bottle numbers are still remaining in the pharmacy, click on *Drug Inventory* (see figure 6.1a).

6.2a Study Drug Inventory (figure)



The *Drug Inventory* has three options (see figure 6.2a). To view the study drug bottle numbers that have been dispensed, enter '**1**' to have them sorted by bottle number (see figure 6.2b), or enter '**2**' to have the dispensed study drugs sorted by patient ID. The listing also displays the visit at which the drugs were dispensed and the date that they were dispensed in the data system. Since the study drugs may be dispensed in the data system prior to the patient's visit, this may not be the actual date that the study drugs were dispensed to the patient.

6.2b Dispensed study drugs sorted by bottle number (figure)



Data System NASH CRN - Nonal

Study drug inventory at IU

Type of inventory [ ] 1 = study drugs dispensed, sorted by bottle number
2 = study drugs dispensed, sorted by patient ID
3 = available study drugs

Study [ ] 7 = FLINT

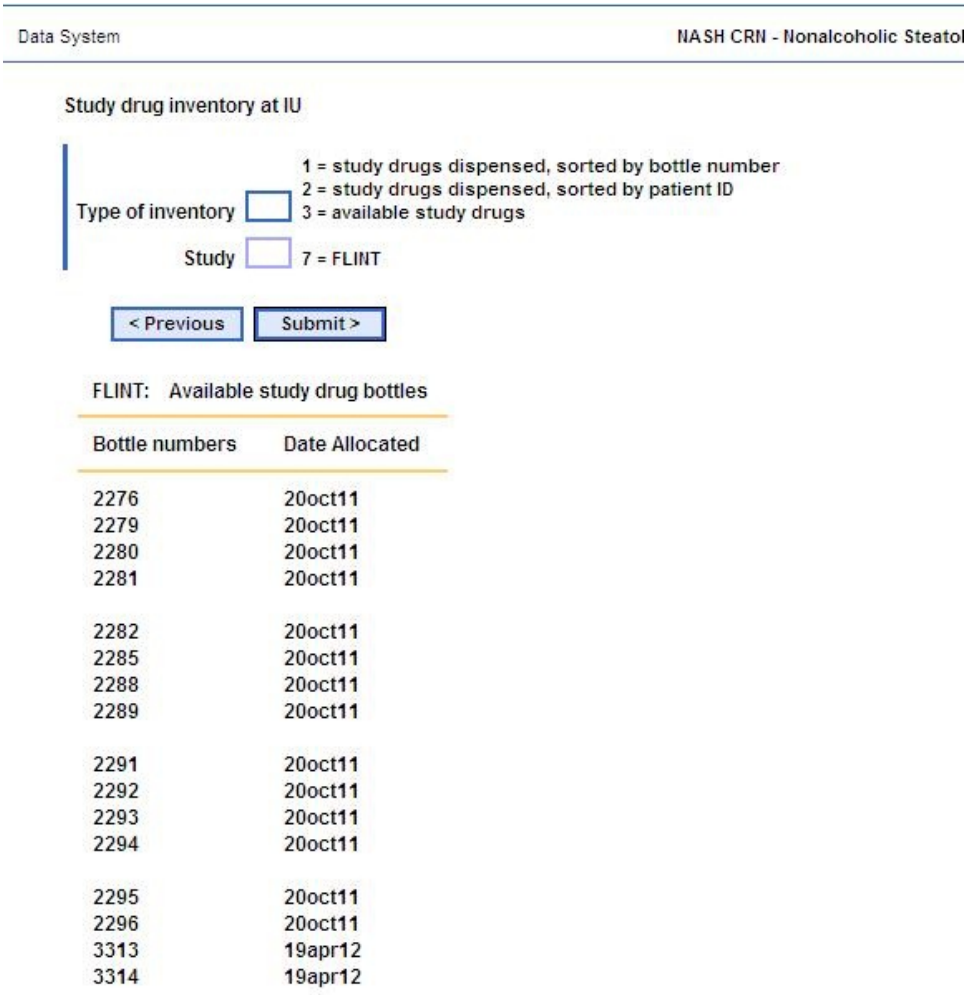
< Previous Submit >

FLINT: Study drugs dispensed:

Bottle numbers	Patient ID	Visit	Date Dispensed
1481	3284	rz	24may11
1482	3277	rz	02May11
1483	3277	rz	02May11
1484	3284	rz	24may11
1485	3284	rz	24may11
1486	3277	rz	02May11
1487	3275	rz	18may11
1488	3286	rz	07Jun11
1490	3286	rz	07Jun11
1491	3286	rz	07Jun11
1492	3275	rz	18may11
1493	3290	rz	12Jul11
1494	3275	rz	18may11
1495	3283	rz	27may11
1496	3290	rz	12Jul11
1497	3290	rz	12Jul11

The third option displays the study drug bottle numbers that have not been dispensed yet and are available at the clinic pharmacy (see figure 6.2c). The listing shows the bottle numbers and the date allocated, which is the date that drugs were received by the pharmacy. At the end of the list of study bottle numbers is the count of how many bottles remain in the inventory. The DCC keeps track of how many bottles are remaining in the clinic pharmacy and will periodically have additional study drugs shipped to the pharmacy.

6.2c Available study drugs (figure)



7. Data entry of forms

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7.1. Instructions for data entry

The data forms completed for NASH CRN participants constitute the official database for the specified study. All of the NASH CRN study findings and results will be derived from analyses of the electronic database. Responsibility for data entry resides at each clinical site.

It is extremely important that the computerized data files match the information recorded on the paper forms. All edits to the paper forms must be dated, initialed, and include a brief explanation as to why an item was changed by the appropriate staff member. If a change is made to a paper form, the change must be made to the electronic record also. These changes, first to the paper form and then to electronic record, should be made as simultaneously as possible.

Data entry operators are key to fulfilling these quality assurance requirements. If the electronic database is incorrect, the conclusions drawn from analyses of the database are likely to be incorrect.

The NASH CRN data system has several features designed to promote accuracy of data entry:

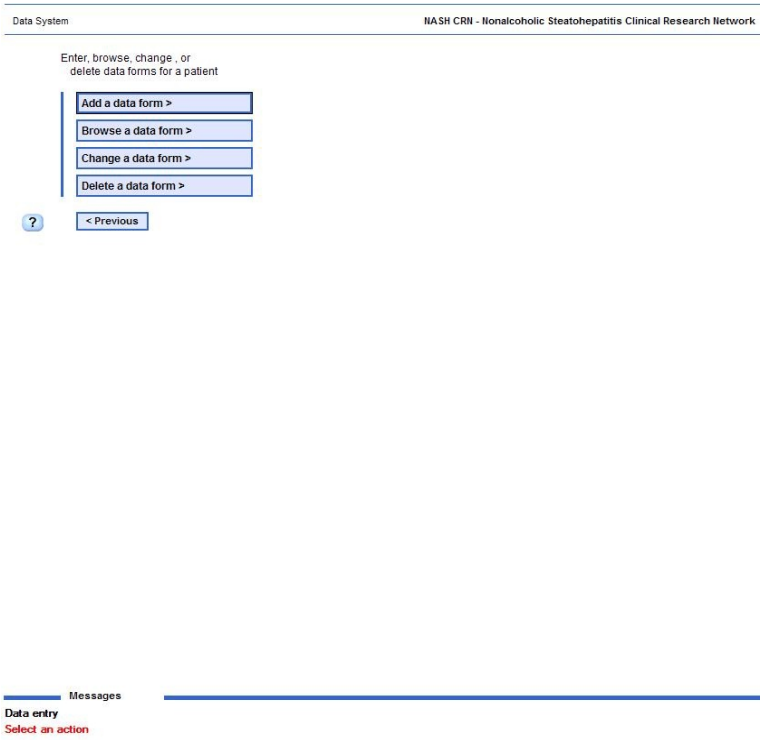
- Range checks at the time of data entry
- Consistency checks at the time of data entry
- Double keying of all data items (except General Comments), with checks on agreement between keyings

These features may slow the data entry process because the data entry operator will have to resolve problems in order to complete the keying. Hence, it is to everyone's advantage to complete the paper forms carefully, correctly, and accurately so that they are as free of problems as possible.

NOTE that data can be saved only for a form keyed twice with no data entry errors. You cannot save your work in the middle of keying a form.

To add, browse, change, or delete a form, click on the *Data entry* task on the MAIN TASKS menu screen (see figure 2.4a). The DATA ENTRY menu screen will appear as in figure 7.1a. To select a data entry option, click on the option's button and the data entry task screen will be in view. Clicking on the *Previous* button returns the user to the MAIN TASKS menu.

7.1a DATA ENTRY menu screen (figure)



To initially key a form's data, click *Add a data form* on the DATA ENTRY menu, and then enter the key variables from Section A of the form (see figure 3.4b). These are the variables that uniquely identify the form data.

- Patient ID - four digit number that uniquely identifies the NASH CRN study participant (item 2 on every form)
- Patient code - three character code that uniquely identifies the NASH CRN study participant (item 3 on every form)
- Date of form - date form was completed, i.e., the visit date or the date that the hard copy form was completed, NOT the data entry date (item 4 on every form)
- Visit code - e.g., **t0, t048, t096, f144, f192**, ... (item 5 on every form)
- Form + revision code - the form code and revision number, e.g., **rg1**, **1r1**, ... (item 6 on every form)
- Study number - specified study number (e.g., **6** for Database 2, **7** for FLINT, **8** for CyNCh) (item 7 on every form)

Each data item must be keyed twice. After entering this information, hit **ENTER** or click on *Submit* to access the data entry screen for the form. Note that after the key variables for the RG form are submitted, a prompt appears requesting confirmation of the study. Type the study name (e.g., CyNCh, FLINT or database 2 for the adult and pediatric NAFLD Database 2 studies).

Data should be keyed **exactly** as they appear on the form. After keying a field, press **ENTER** or click in the next box to advance to the next data field. When there are gaps between fields, use the scroll bar and click on the field to be keyed rather than pressing the **ENTER** key repeatedly. To go to a previous field, either click in that box or press **shift-Tab** to go back through the fields.

The final screen for each form has a General Comments area where excess comments, marginal notes, or other comments may be keyed.

Data entry keying of various types of fields (see Appendix 11.3 for a summary table):

Generally, you will completely fill the data entry space provided for each response; the exceptions to this are, "Other *(specify)*" responses (which may not require the 35 characters allowed), the General Comments fields (which may or may not include responses) and special response codes: **r** (refused), **d** (don't know), **m** (missing), **n** (not applicable), **?** (query: temporarily missing). Appendices 11.4 and 11.5 provide additional information for special response codes.

Signatures are not keyed — type **1** if the signature is present; type **?** if the signature is not present.

Numeric fields must be filled completely; the staff members recording data items on forms should use leading and trailing zeros as needed. For example, hemoglobin (item 17 on Form LR1) has the format _ _ • _. Suppose the lab report gives a value of 1.0. The person recording the data on the form should write in 0 1 • 0. The data system operator keys **010**. Note that punctuation marks for numeric data (decimal points and commas) are not keyed.

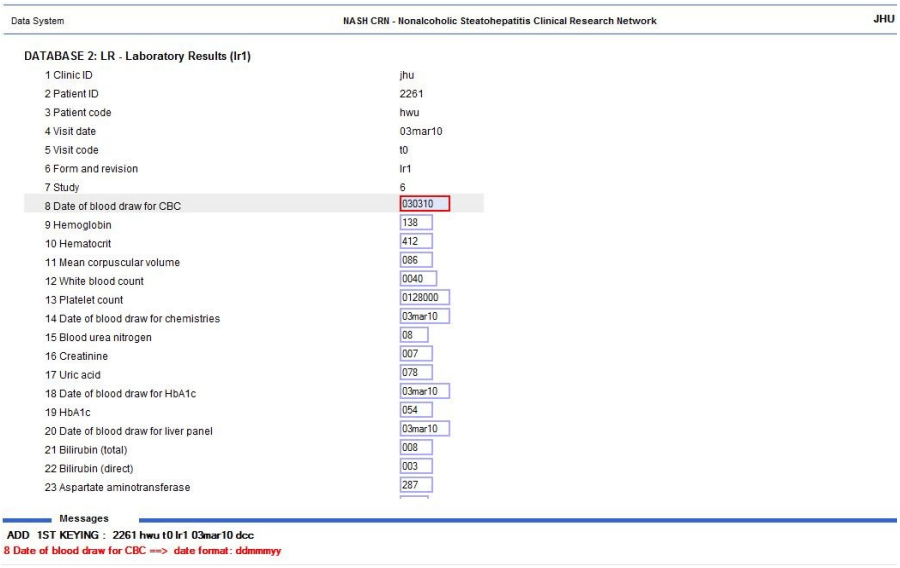
For **"all that apply" items** (such as item 49 on Form BG1), key a **1** if the item is checked; if the item is not checked, leave the field for that item blank. There must be at least one response item keyed. The program will not allow required items to be bypassed by leaving blank.

The **General Comments fields** are used to record the excess response in an "Other *(specify)*" item that exceeds the 35 characters allowed, and any marginal notes or other comments. The General Comments area includes 5 lines each accepting 75 characters and is the last screen to appear when keying a form. This is not a required data item for system edit checks; however, there are situations in which information must be keyed or a DCC audit check will be initiated.

Note that **use of a question mark symbol**, '?', in a comment or specify item field will result in an edit message; instead of keying a question mark, indicate the uncertainty in the response by keying 'possibly', 'quest', 'maybe', etc. in the comment or specify field.

After an item is keyed and the **ENTER** key pressed, the system will perform a series of checks to see that responses are in the correct format, within the allowable range, and consistent with other responses provided on the form. When these checks find an error, the error must be corrected before the data entry operator can continue keying other items. A message at the bottom of the screen will help to identify the error. Figure 7.1b shows the error message received when the date for item 8 on the LR form was keyed using an invalid format.

7.1b Shows the error message received when the date for item 8 on the LR form was keyed using an invalid format (figure)



Error messages:

The error must be corrected before the data entry technician can continue keying other items, continue to the second data entry, or save the data to the database.

An ERROR message can be resolved in one of three ways: by correcting the keyed value, by keying a **?** (query code) to indicate that the item is under review, or by keying a correction to an associated item that will render the data consistent. When an ERROR message appears, the data entry operator should check the form to be sure that the data were keyed as written on the form. If the data were keyed as written, but an error is noted on the form (e.g., an item was answered that should have been skipped), the data entry operator may enter **?** for the item(s) in question, and the ERROR message should disappear. These should be flagged on the hard copy to the appropriate staff member's attention. The items marked **?** will appear in edit queries from the DCC for resolution until the **?** is replaced with a response or other data entry code. Appendices 11.4 and 11.5 give more information on missing value codes and their appropriate use.

Alternatively, if the person who completed the form is available, the item(s) in question may be edited on the paper form (every edit must be initialed and dated by the appropriate staff member) and the corrected data then entered. **Edits must be verified — the data entry tech should not simply change the data on the form to what s/he thinks the response should be.** This is a serious action that could cast doubt on all of that clinic's results.

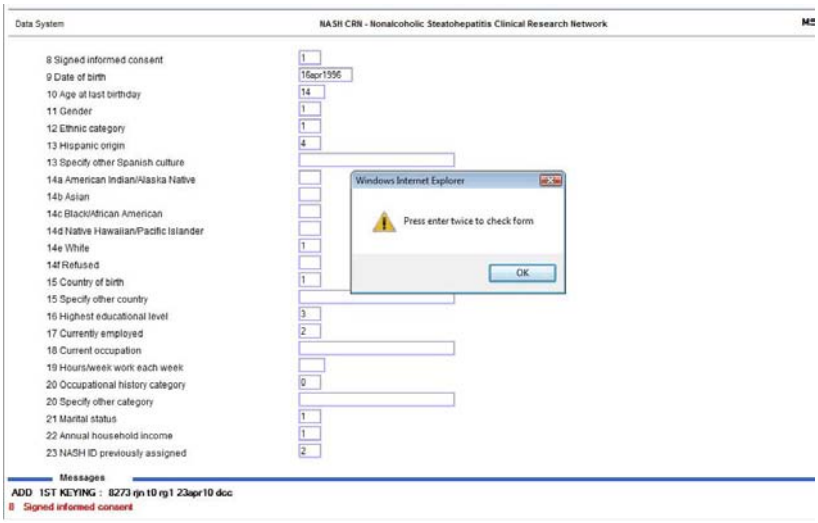
If the data are keyed correctly and the form is completed correctly and there is still an error, write down the error message, print the screen, key **?** for items that you cannot key as completed, and contact the DCC for further assistance.

Appendix 11.6 is a summary table of the most common types of data error messages and their resolutions.

Double data entry:

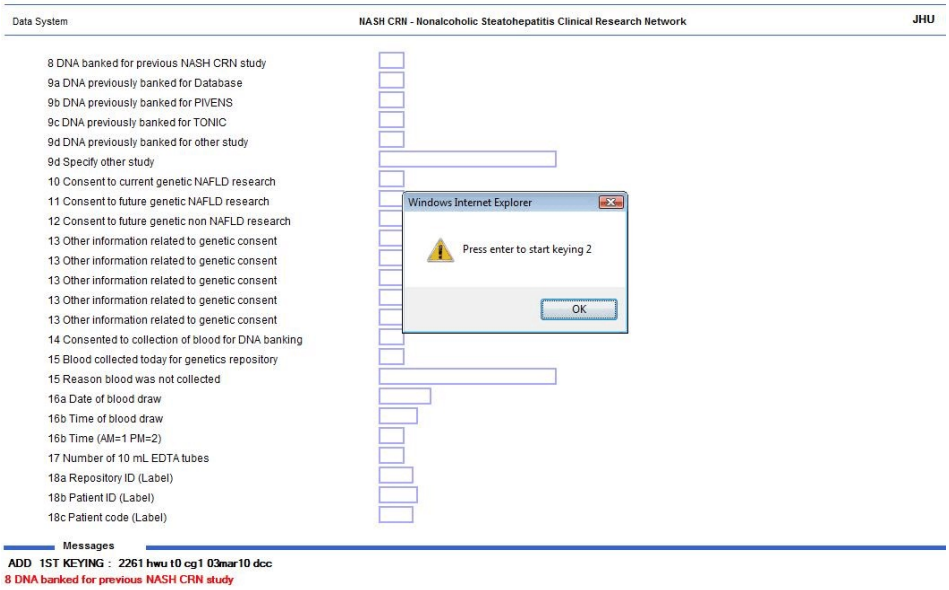
The data for each form must be keyed twice. After entering the last item of the first keying, a pop-up window appears with instructions to press ENTER twice to check the first keying for inconsistencies and other data errors (see figure 7.1c).

7.1c Form check after first data entry keying (figure)



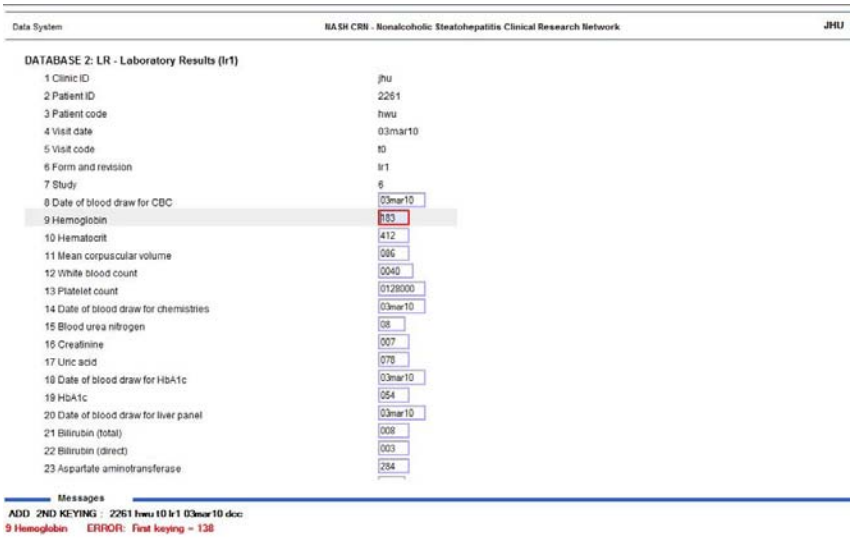
Once all consistency checks from the first keying are resolved, a pop-up window appears with instructions to press ENTER once more as in figure 7.1d. The system then saves the responses from the first keying, clears the responses from the data entry screen, and sets the cursor to begin the second keying.

7.1d Clear screen to begin second data entry keying (figure)



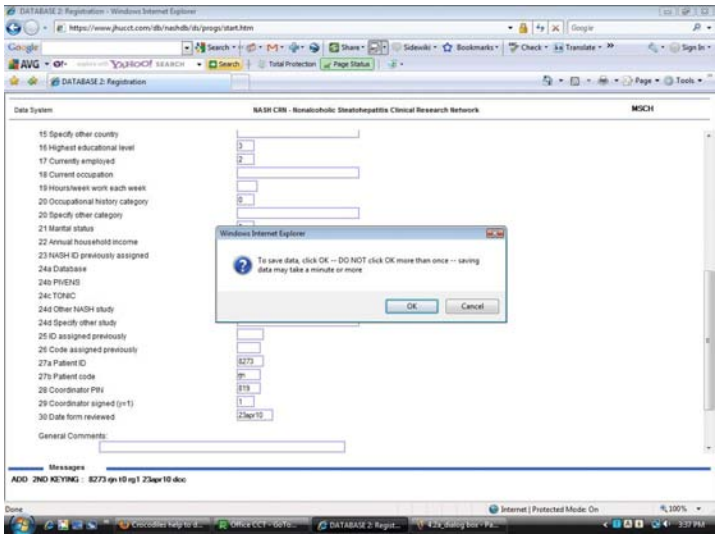
If the second keying of an item does not agree with the first keying, the value of the first keying will be displayed in the lower left corner of the screen, as in figure 7.1e below. If the first keying was correct, enter the correct value and press **ENTER**. If the second keying was correct, press **ENTER** to continue the checks.

7.1e First and second keying do not agree (figure)



Once all data entry errors have been corrected, click the *OK* button ONCE in the pop-up window shown in figure 7.1f to save the data entry values to the electronic database.

7.1f Save data to the database (figure)



Confirmation screen:

After a form has been keyed twice, all consistency checks are passed, and the data saved by clicking on the *OK* button, a confirmation screen appears (see figure 4.1c). This confirms that the data for that form have been saved in the electronic database.

Click *Continue* and the screen returns to the MAIN TASKS menu.

After keying the form, the data entry tech should check the "keyed" box on the first page of the form and initial and date the form hard-copy.

Summary reminders:

(1) Guidelines for the keyboard during data entry:
- **Num Lock** on, **Caps Lock** off, **Insert** off
- Use numeric keypad to ENTER numeric data
- Press **ENTER** after each item
- Press **Shift-Tab** or use the mouse to go back to previous items
- Use the mouse to navigate around the screen

(2) Data can be saved only for a complete form and only after double data entry. You cannot save your work in the middle of a form.

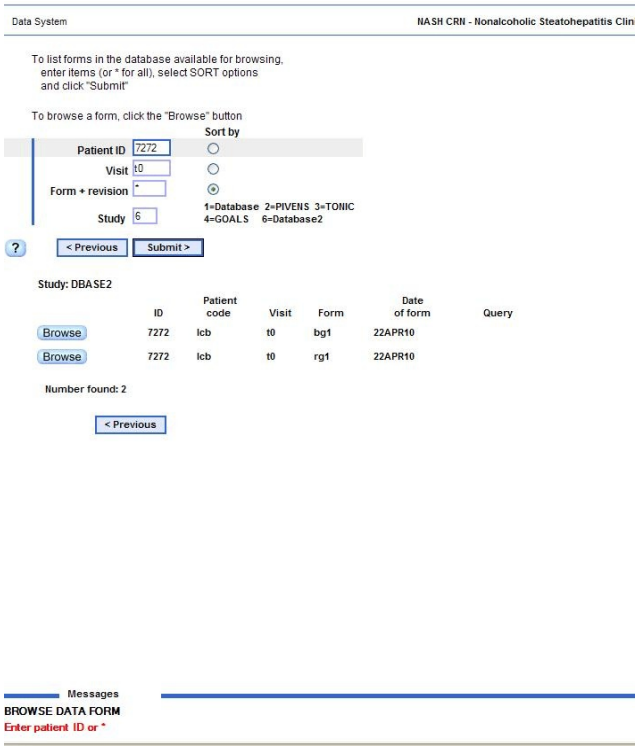
(3) The data entry tech should initial and date the form after the confirmation screen appears.

7.2. Browsing data

After a form is keyed and saved, it is possible to look at what was keyed in the data system. The safest way to do this is to browse or look at the form without being able to make changes to it.

1. From the DATA ENTRY screen (see figure 7.1a), click on *Browse a data form*.
2. Key the information that identifies the form to be browsed: Patient ID, visit code, form + revision code, and study number in the browse data form prompt screen.
3. Key an asterisk (*) to request all items for that identifier.
4. Click the *Submit* button and the browse data form screen (see figure 7.2a) is displayed.
5. Click the *Browse* button to the left of the forms listed to see the contents of the form.
6. A screen with all of the data for that form as it appears in the database will be displayed, but the form data may not be changed.

7.2a Browse data form (figure)

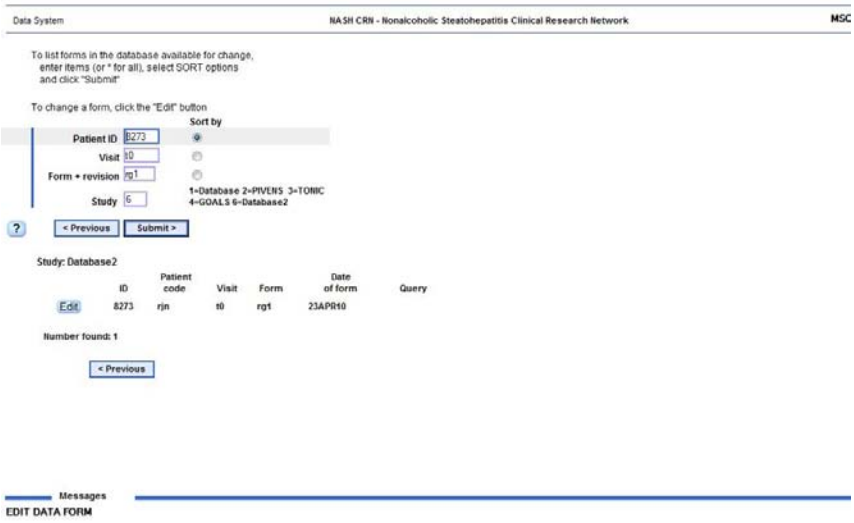


7.3. Changing data

To correct an error or update information on a form that has been keyed and saved, the Change task is used.

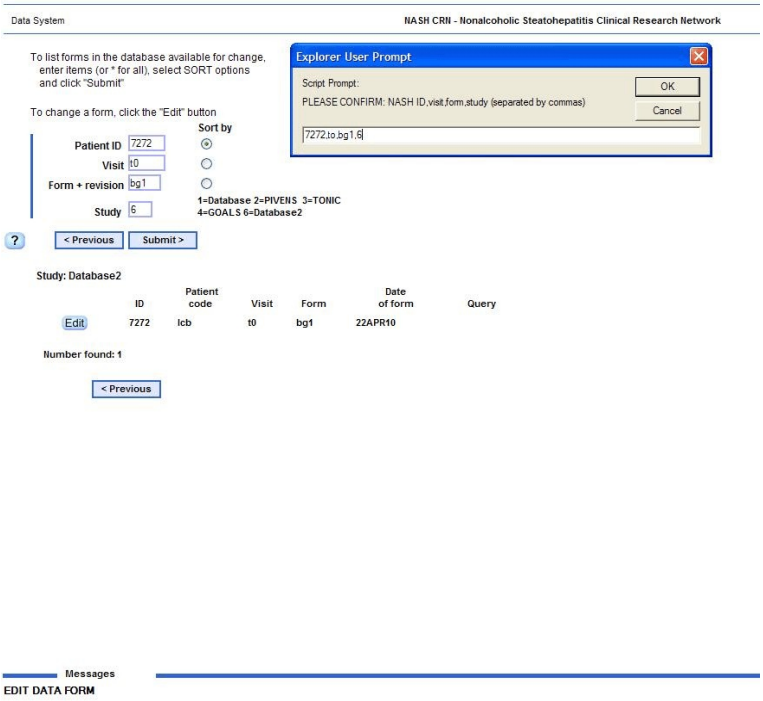
1. From the DATA ENTRY screen (see figure 7.1a), click on *Change a data form*.
2. Key the information that identifies the form to be edited: Patient ID, visit code, form + revision code, and study number in the change data form prompt screen.
3. Key an asterisk (*) to request all items for that identifier, e.g., to retrieve all forms for a specified participant, in a given study, key the Patient ID, the study number, and then key asterisks for visit code and form + revision code. Keying all asterisks and a study number retrieves all forms in the data system for the specified study.
4. Click the *Submit* button and the change data form screen (see figure 7.3a) is displayed.

7.3a Edit data form (figure)



5. Each form on the resulting list will have an *Edit* button to the left of the form list. Click on this button to display the contents of a form.
6. A script prompt window screen requests that the patient ID, visit, form, and study number items (separated by commas) be re-entered as verification that the form you clicked on is the form you want to change (see figure 7.3b).

7.3b Edit data form - verification of record ID (figure)



7. A screen with all of the data for that form as it appears in the database will be displayed.
8. To change an item: delete the old data in the specified item's entry cell and type in the new information. Press ENTER when finished.
9. All consistency checks are performed by the data system; if no errors are flagged, then press ENTER twice (to save the data) and click on *OK*.
10. A confirmation screen for the changed form record will appear.

If the change in the data system occurs as a result of changes to the original hard copy form, that change must be reflected on the original form (incorrect item crossed out, dated, initialed, and reason written in margin).

The data entry technician should initial and date the hard copy form once the data change has been keyed, saved, and the confirmation screen has appeared.

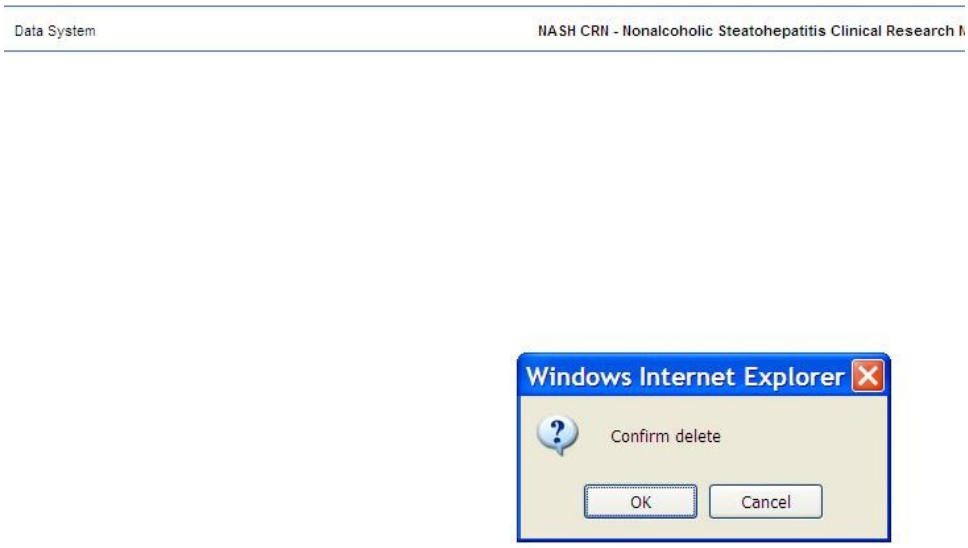
7.4. Deleting data

If an entire form is found to be incorrect (e.g., data entered for the wrong participant or key variables were entered incorrectly), the form must be deleted.

1. Go to the DATA ENTRY screen (see figure 7.1a) from the MAIN TASKS menu.
2. Click on *Delete a data form*.
3. In the prompt screen (see figure 7.4a), enter the key identifiers for the form twice.
4. Click on *Submit*.
5. After clicking Submit, a pop-up window appears on the screen asking you to confirm the delete (see figure 7.4b). After clicking OK, a confirmed screen for the deleted record will appear.

7.4a Delete a data form screen(figure)

7.4b Delete a data form confirm screen (figure)



Use this function with caution.

Remember that once a participant's ID number, patient code or registration date for a study has been assigned after the RG form is keyed and saved, these codes cannot be changed. **A saved RG form cannot be deleted**. If the visit date is incorrect on the saved RG form, please notify the DCC.

8. Printing

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8.1. Blank forms or form sets

Data forms should be printed from the NASH CRN website:

- The form sets should be printed from the NASH CRN website by clicking on *Studies* from the left-hand menu, the selected study link, *Data forms*, and then *Print blank form sets and flash cards*. Then choose the form set needed *(i.e., Baseline (t0) visit)* form set for either Adults or Children in Database 2 or Screening (s) visit in FLINT, or CyNCh.

- Individual forms can be printed from the NASH CRN website by clicking on *Studies* from the left-hand menu, the selected study link, Data forms, and then *Patient forms*. Then click on the form you need to print.

NOTE: Your internet browser's POP-UP blocker must be set to OFF.

Please use the above methods to print the forms or form set needed for each participant just prior to each screening or follow-up visit. This ensures that the forms being used will always be up to date. The forms in the form sets will be in alphabetical order.

8.2. Labels

The Print Labels function will enable printing of the labels needed for data collection forms and whole blood collection tubes at each participant visit. Please note that the DCC will supply a set of pre-printed ID number and name code labels to be used on the RG form, as well as labels for cryovials and slides. These labels cannot be printed from the data system.

The sheet of labels displayed by the data system will be in a PDF file format, which can then be printed using the Adobe PRINT icon or File/Print menu. There is one set of labels per participant per visit per study, which will include all the labels needed for the data forms and whole blood collection tubes at a particular study visit.

Whole blood collection administrative forms
- Blood for serum (red-gray top SST)
- Genetic consent and blood for plasma (green top sodium heparin)

Whole blood collection tubes
- Blood for serum (red-gray top SST)
- Blood for plasma (green-top sodium heparin)
- Blood for the Genetics Repository (2 purple-top NaEDTA)

Type of labels to use:

Use MACO Laser/Ink Jet White All-Purpose/Address Labels, MACO # MML-5000 1" x 1 ½" labels, 50 per page, 5000 per box, to be supplied by the clinic. Find a supplier by visiting www.maco.com/where-to-buy.html , or by doing an internet search for "MACO ML 5000 labels," or by checking with the clinic's office supplier. PPM 12 gives more details concerning the purchase and use of labels.

Screening visit labels:

The labels for a screening visit t0 or s should be printed after registering a participant. Once you have keyed the Registration (RG) form and resolved all error messages and edits, a confirmation screen will appear confirming that you have successfully registered the participant. To print labels:

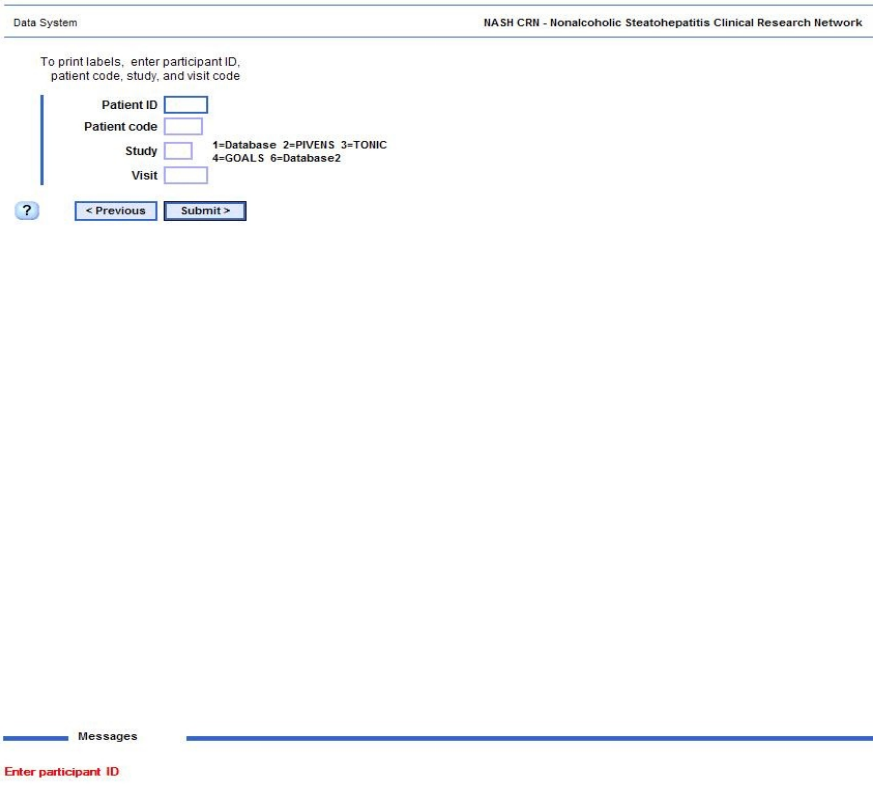
1. **Make sure your internet browser's POP-UP blocker is set to OFF**
2. Click on the *Print* button next to "*Click here to print Screening labels*" (see figure 4.2a)
3. A screen with the participant's labels appears in a PDF file format.
4. Insert one sheet of labels in the printer's single sheet feeder
5. Print the labels using the Adobe PDF PRINT icon or the PDF File/Print menu
6. **Uncheck** the following options when the PDF "Print" confirmation appears:
   - Shrink oversized pages to paper size
   - Expand small pages to paper size
   - OR Fit to printer margins
   - Auto-rotate and center pages

Follow-up visit labels:

Once a participant is found to be eligible and is enrolled in the Database 2, labels for the follow-up visits may be printed. To print these labels:

1. Go to the MAIN TASKS menu screen (see figure 2.4a)
2. Click *Print*
3. Click *Labels*
4. Key the Patient ID, Patient code, study number, and the specific visit code. (see figure 8.2a)
5. Click *Submit*
6. Print labels following the same directions given above for printing the screening visit labels.

8.2a Print Label screen (figure)



If a patient's labels are lost or the screening visit labels were not printed from the RG form confirmation page, additional labels can be printed at any time for that participant and visit from the PRINT menu screen.

9. Listings

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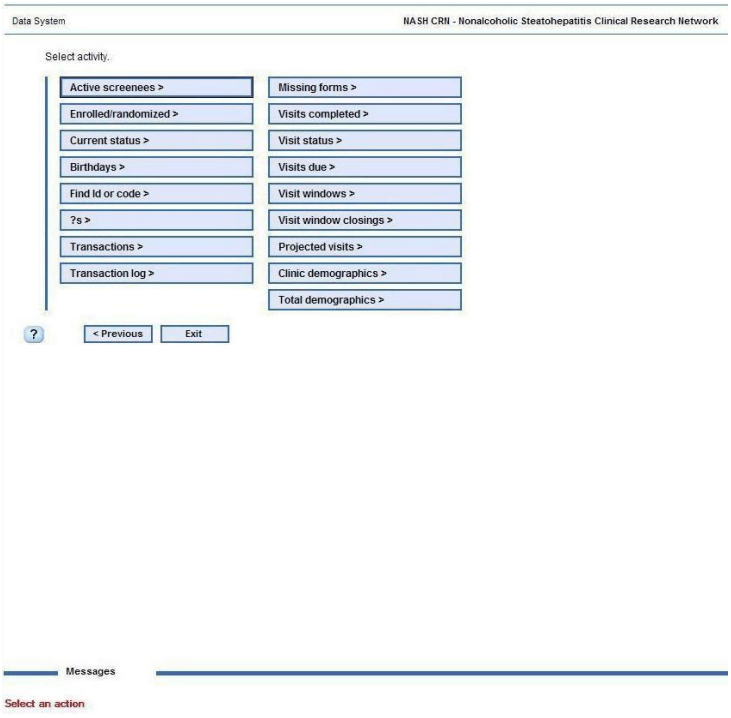
9.1. LISTINGS menu

The LISTINGS menu screen displays various activities available through the web-based data management system to produce automated listings or reports. These windows can then be printed if desired.

To access this menu, first click on *Listings* in the MAIN TASKS menu (see figure 2.4a). The screen shown in figure 9.1a will appear.

9.1a LISTINGS menu screen (figure)



Select an activity by clicking on the button for that activity. Each activity is described in detail in the remainder of section 9. Using the asterisk **(*)** code when allowed will select all patients, visits or forms, respectively. The study number codes are **6** for Database 2, **7** for FLINT, **8** for CyNCh.

Clicking on the *Previous* button returns to the MAIN TASKS menu. Clicking on the *Exit* button will exit the system and return to the desktop.

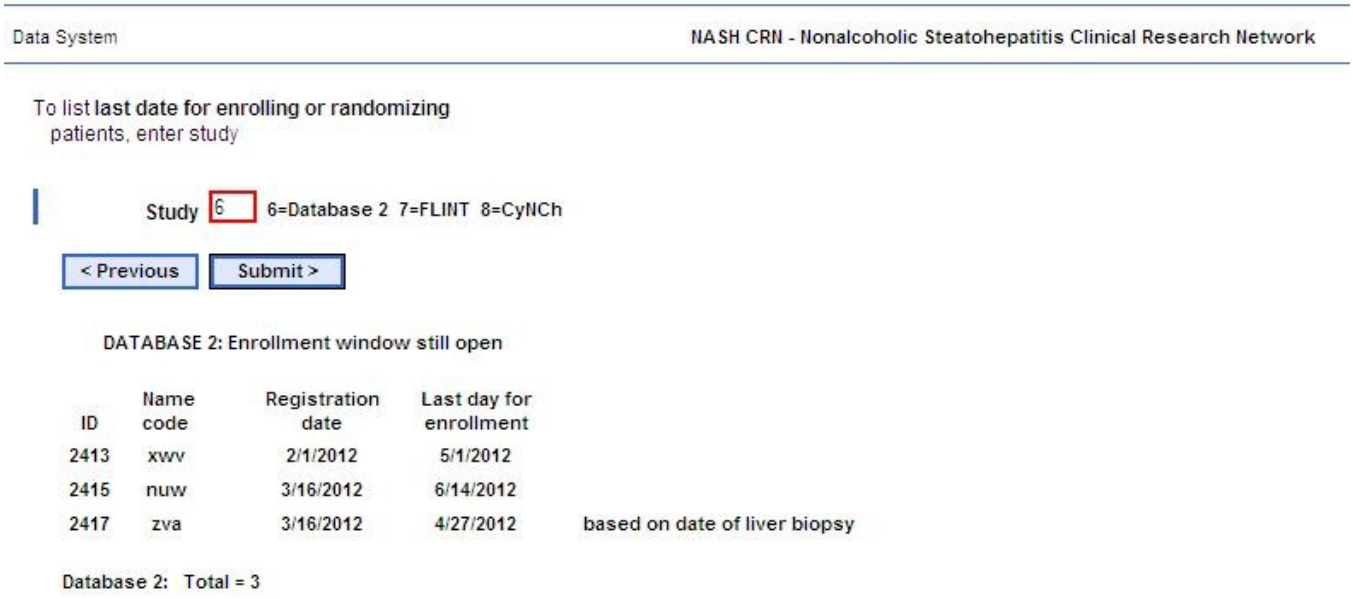
Lists and reports can be printed using the PRINTER icon.

9.2. Active Screenees listing

The Active Screenees option will produce a list of the patient IDs, patient codes, registration dates, and last possible date for enrollment for all participants currently in active screening for a specified study (i.e., registered patients who have not been enrolled into a NASH CRN study (e.g., Database 2) or randomized into a trial (FLINT or CyNCh) or who have not been closed out of the study).

To display the Active Screenees listing, click on *Active screenees* on the LISTINGS menu. Key the study number, and the list will be displayed as in figure 9.2a.

9.2a Active Screenees listings (figure)

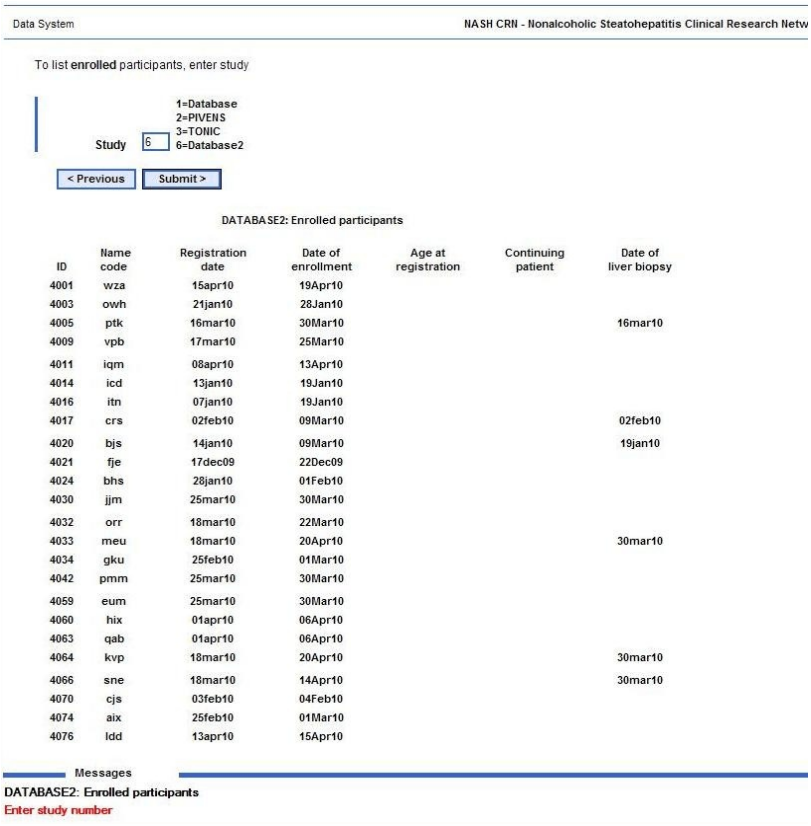


9.3. Enrolled/Randomized listing

The Enrolled/Randomized option will produce a list of the patient IDs, patient codes, registration dates, the dates of enrollment/randomization and other information for all participants enrolled/randomized in the specified study.

To display the Enrolled/Randomized listing as in figure 9.3a, click on *Enrolled/randomized* from the LISTINGS menu. Key the study number and click on *Submit*. Note that enrolled participants are listed for the Database 2. Randomization only occurs for a treatment trial.

9.3a Enrollment/Randomized listing (figure)



9.4. Current Status listing

The Current Status option will produce a list of all participants registered in any NASH CRN study at your center, the current study in which the participant is registered, the participant's current status (whether the participant is in screening, in follow-up, or is ineligible), whether or not the participant is registered in another NASH CRN study and what the participant's status is in that other study. If the current status of a participant is ineligible (INEL) or closed out (CO) and is followed by an asterisk (*****), the Database 2 Enrollment (EN) form or the Database 2 Closeout (CO) form has not been keyed; therefore, the participant is assumed to be ineligible because the screening window has closed or they are assumed to be closed out because they have enrolled in another study.

To display the Current Status listing as in figure 9.4a, select *Current status* from the LISTINGS menu.

9.4a Current status listing (figure)

Data System NASH CRN -

Current status for all patients as of 4/4/2012

< Previous

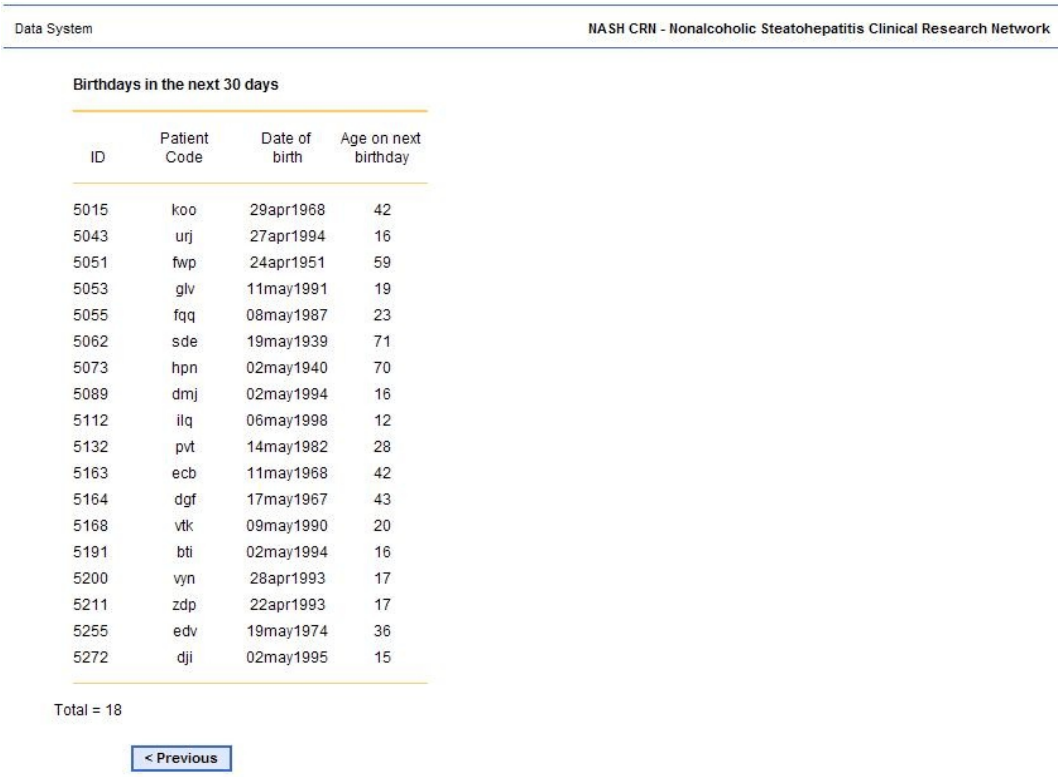
NASH ID	Current Study	Current Status	Database 2 Status	FLINT Status
2009	Database 2	FU	FU	
2013	Database 2	FU	FU	
2021	Database 2	FU	FU	
2022	Database 2	FU	FU	
2026			COtrial	
2030	Database 2	FU	FU	
2033	Database 2	FU	FU	
2038	Database 2	FU	FU	
2042	Database 2	FU	FU	
2057	Database 2	FU	FU	
2058	Database 2	FU	FU	
2061	Database 2	FU	FU	
2069	Database 2	FU	FU	
2084	Database 2	FU	FU	
2088	Database 2	FU	FU	
2089	Database 2	FU	FU	
2099	Database 2	FU	FU	
2100	Database 2	FU	FU	
2104	Database 2	FU	FU	
2106	Database 2	FU	FU	
2108	Database 2	FU	FU	
2110	Database 2	FU	FU	
2113	Database 2	FU	FU	
2115	Database 2	FU	FU	
2118	Database 2	FU	FU	
2120	Database 2	FU	FU	

9.5. Birthdays listing

The Birthdays option will produce a list of birthdays occurring in the next 30 days and the participant's age at their next birthday for all participants enrolled in any NASH CRN study at your center.

To display the Birthdays listing as in figure 9.5a , select *Birthdays* from the LISTINGS menu

9.5a Birthdays listing (figure)

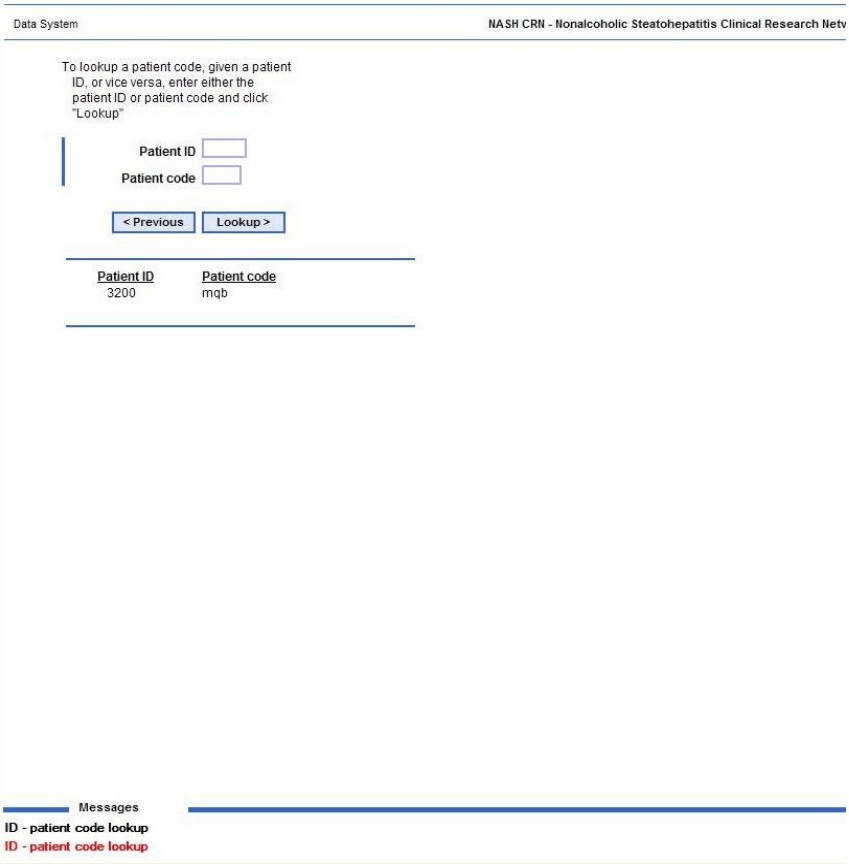


9.6. Find Patient ID or Code (look up) function

The Find ID or Code function will display a participant's patient code for a given ID number, or the patient ID number for a given patient code.

To access the Find ID or Code function, go to the LISTINGS menu, click on *Find ID or code*, key either the Patient ID or Patient code and click on the *Lookup* button. The information is displayed in the window as in figure 9.6a below.

9.6a Find ID or Code function (figure)



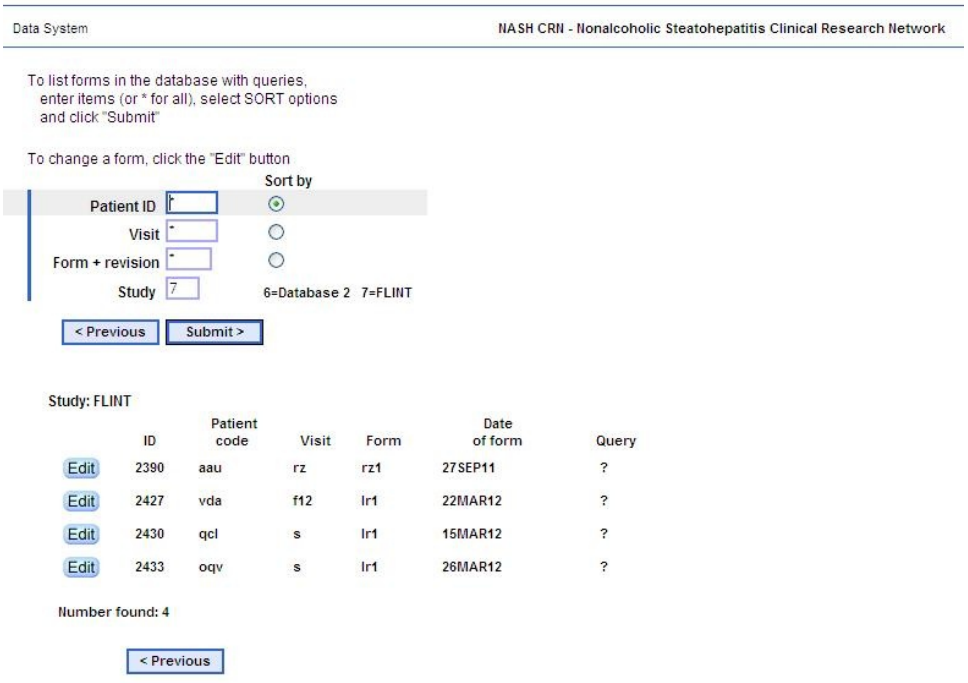
9.7. Outstanding Queries (?s) report

The Outstanding Queries (?s) report displays a list of forms with unresolved queries. If a **?** was entered for any item on a data form, the form is considered incomplete. The DCC will periodically provide a listing of these forms to clinics for resolution. In the interim, clinics can produce a list on their own using the Outstanding Queries (?s) report. Appendix 11.5 provides detailed information on the use of the query code.

To display the report as in figure 9.7a, go to the LISTINGS menu, click on *?s*. Key the patient ID, visit, and/or form + revision and study codes of the form(s) you wish to see on the Outstanding Queries (?s) list. To list all of the forms with **?**'s for a specified study, enter an asterisk (*****) for patient ID, visit, and form + revision items.

Each form on the resulting list will have an *Edit* button. Click on this button to bring up the form in CHANGE mode. Re-enter the patient ID, visit, form and study codes (separated by commas) in the script prompt window screen as verification that this form is the correct form to be changed. The data in the form can now be edited using the CHANGE function of the data system (see section 7.3).

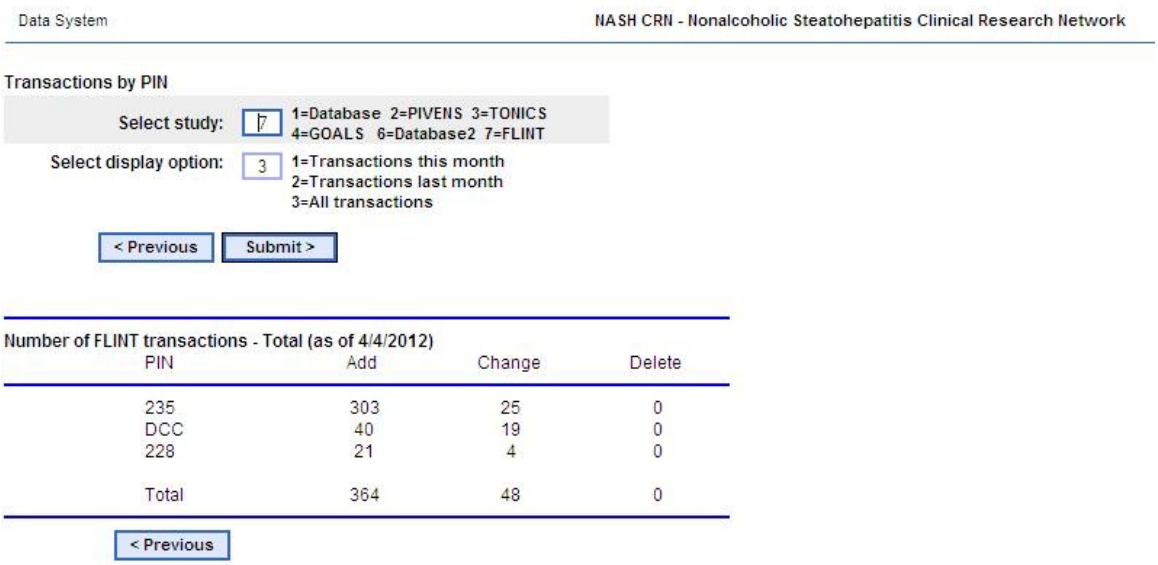
9.7a Outstanding Queries (?s) report (figure)



9.8. Transactions report

The Transactions report provides a summary of data entry activity at your clinic for a specified study. To use the transactions report, select *Transactions* from the LISTINGS menu. To view a summary of forms entered, changed, and deleted in the current month, key the study number and enter a **1** to select the current month display option and click on *Submit*. This lists all of the transactions that have been entered during that month sorted by PIN of the data entry operator. A summary of transactions during the previous month (Display option **2**) and overall (Display option **3**) can also be displayed.

9.8a Transactions report (figure)

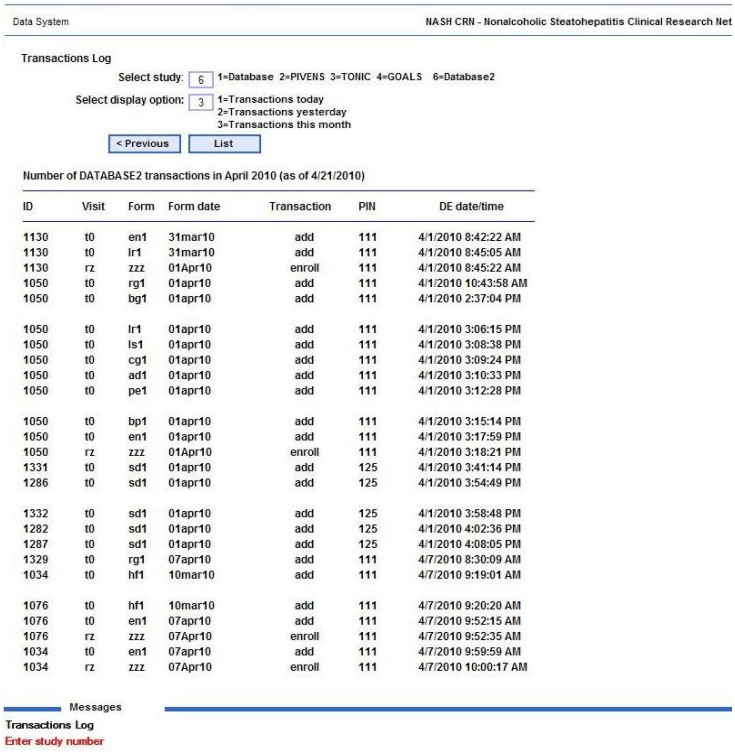


9.9. Transaction Log listing

The Transaction Log listing displays all web transactions done on a specified day (today or yesterday) or for the entire month for a specified study. A list with the patient ID, visit, form, form date, transaction, PIN, and date and time of transaction will be displayed as in figure 9.9a.

To display the Transaction Log listing, click on *Transaction log* on the LISTING menu. Key the study number and the number of the display option (**1**=Transactions today, **2**=Transactions yesterday, **3**=Transactions this month), and click on *List*.

9.9a Transaction Log listing (figure)



Data System — NASH CRN - Nonalcoholic Steatohepatitis Clinical Research Net

Transactions Log

Select study: 6 1=Database 2=PIVENS 3=TONIC 4=GOALS 6=Database2

Select display option: 3 1=Transactions today 2=Transactions yesterday 3=Transactions this month

< Previous | List

Number of DATABASE2 transactions in April 2010 (as of 4/21/2010)

ID	Visit	Form	Form date	Transaction	PIN	DE date/time
1130	t0	en1	31mar10	add	111	4/1/2010 8:42:22 AM
1130	t0	lr1	31mar10	add	111	4/1/2010 8:45:05 AM
1130	rz	zzz	01Apr10	enroll	111	4/1/2010 8:45:22 AM
1050	t0	rg1	01apr10	add	111	4/1/2010 10:43:58 AM
1050	t0	bg1	01apr10	add	111	4/1/2010 2:37:04 PM
1050	t0	lr1	01apr10	add	111	4/1/2010 3:06:15 PM
1050	t0	ls1	01apr10	add	111	4/1/2010 3:08:38 PM
1050	t0	cg1	01apr10	add	111	4/1/2010 3:09:24 PM
1050	t0	ad1	01apr10	add	111	4/1/2010 3:10:33 PM
1050	t0	pe1	01apr10	add	111	4/1/2010 3:12:28 PM
1050	t0	bp1	01apr10	add	111	4/1/2010 3:15:14 PM
1050	t0	en1	01apr10	add	111	4/1/2010 3:17:59 PM
1050	rz	zzz	01Apr10	enroll	111	4/1/2010 3:18:21 PM
1331	t0	sd1	01apr10	add	125	4/1/2010 3:41:14 PM
1286	t0	sd1	01apr10	add	125	4/1/2010 3:54:49 PM
1332	t0	sd1	01apr10	add	125	4/1/2010 3:58:48 PM
1282	t0	sd1	01apr10	add	125	4/1/2010 4:02:36 PM
1287	t0	sd1	01apr10	add	125	4/1/2010 4:08:05 PM
1329	t0	rg1	07apr10	add	111	4/7/2010 8:30:09 AM
1034	t0	hf1	10mar10	add	111	4/7/2010 9:19:01 AM
1076	t0	hf1	10mar10	add	111	4/7/2010 9:20:20 AM
1076	t0	en1	07apr10	add	111	4/7/2010 9:52:15 AM
1076	rz	zzz	07Apr10	enroll	111	4/7/2010 9:52:35 AM
1034	t0	en1	07apr10	add	111	4/7/2010 9:59:59 AM
1034	rz	zzz	07Apr10	enroll	111	4/7/2010 10:00:17 AM

Messages

Transactions Log

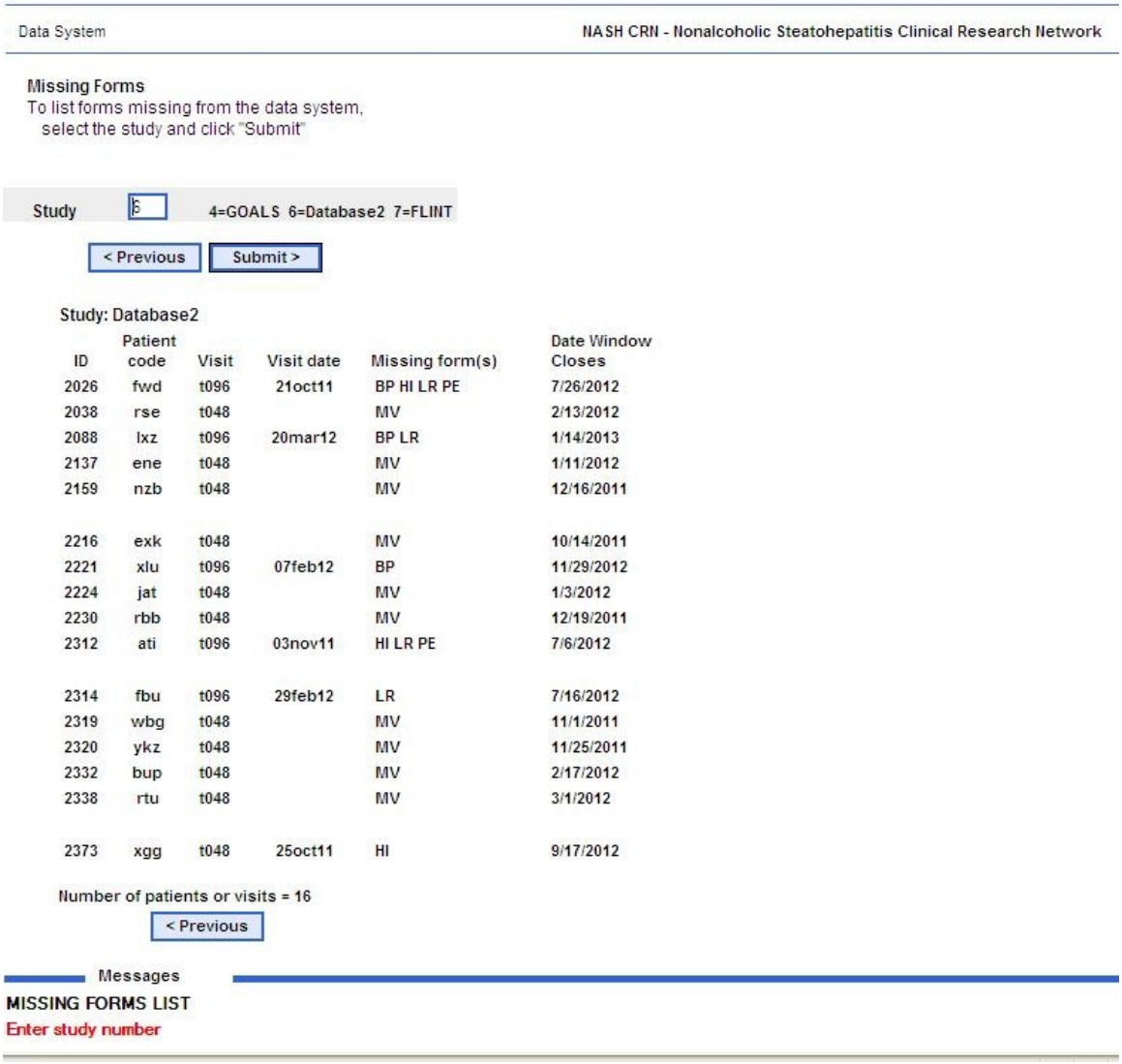
Enter study number

9.10. Missing Forms report

The Missing Forms report lists the patient ID, patient code, visit date (if any part of the visit was completed), and missing forms for participants with missing forms in the specified study. If the visit window has closed and no forms were keyed or drugs dispensed, the Missed Visit (MV) form will be listed as missing. Otherwise, specific forms for that visit that were not keyed will be listed.

To display the Missing Forms report, go to the LISTINGS menu and select *Missing forms*. Key the study number and click on *Submit.*

9.10a Missing Forms report (figure)



Data System — NASH CRN - Nonalcoholic Steatohepatitis Clinical Research Network

Missing Forms
To list forms missing from the data system, select the study and click "Submit"

Study 6 4=GOALS 6=Database2 7=FLINT

< Previous | Submit >

Study: Database2

ID	Patient code	Visit	Visit date	Missing form(s)	Date Window Closes
2026	fwd	t096	21oct11	BP HI LR PE	7/26/2012
2038	rse	t048		MV	2/13/2012
2088	lxz	t096	20mar12	BP LR	1/14/2013
2137	ene	t048		MV	1/11/2012
2159	nzb	t048		MV	12/16/2011
2216	exk	t048		MV	10/14/2011
2221	xlu	t096	07feb12	BP	11/29/2012
2224	jat	t048		MV	1/3/2012
2230	rbb	t048		MV	12/19/2011
2312	ati	t096	03nov11	HI LR PE	7/6/2012
2314	fbu	t096	29feb12	LR	7/16/2012
2319	wbg	t048		MV	11/1/2011
2320	ykz	t048		MV	11/25/2011
2332	bup	t048		MV	2/17/2012
2338	rtu	t048		MV	3/1/2012
2373	xgg	t048	25oct11	HI	9/17/2012

Number of patients or visits = 16

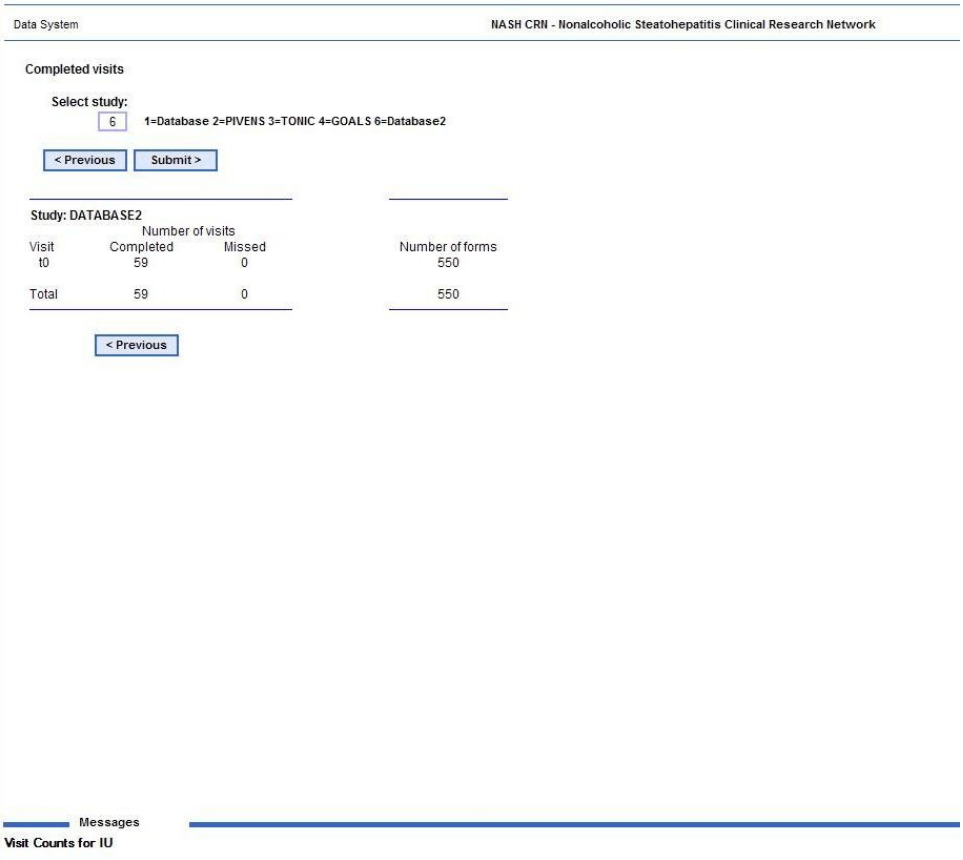
< Previous

Messages
MISSING FORMS LIST
Enter study number

9.11. Visits Completed report

The Visits Completed report provides a count of the number of visits completed, visits missed, and the number of forms data entered for each visit code and overall for the specified study. To view the Visits Completed report, select *Visits completed* from the LISTINGS menu. Key the study number. Click on *Submit* and the list of the visits completed and the number of forms keyed for a given NASH CRN study is displayed as in Figure 9.11a below.

9.11a Visits Completed report (figure)

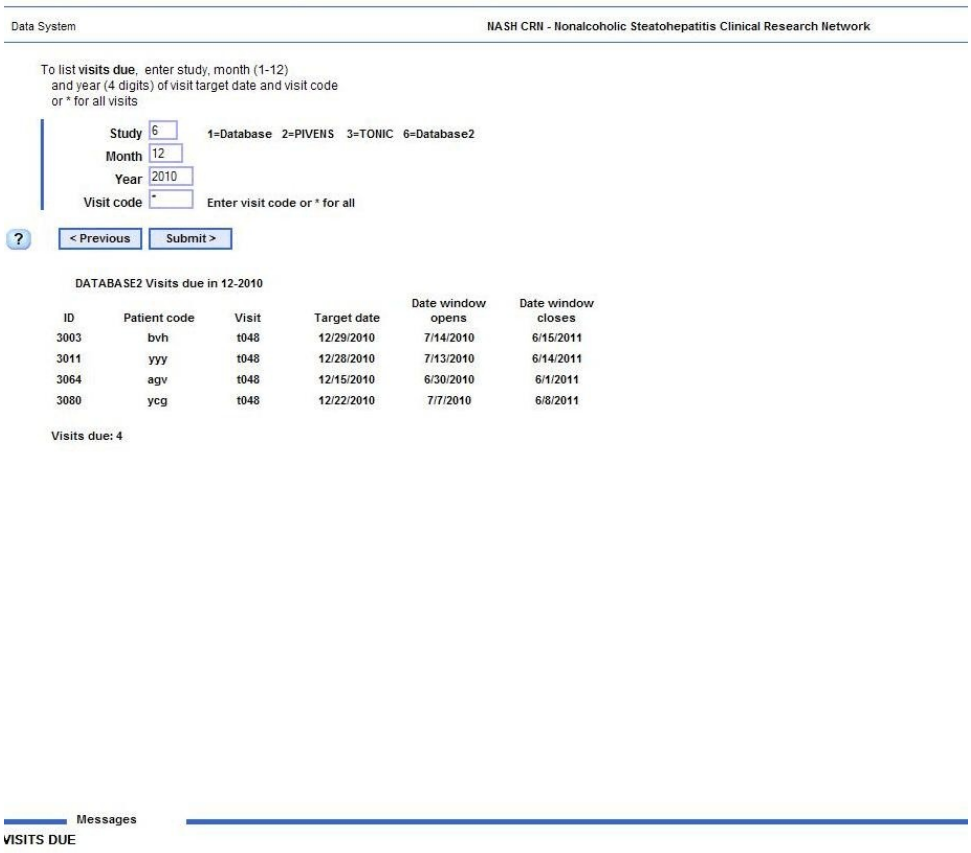


9.12. Visits Due listing

The Visits Due option will produce a list of participants with a visit target date in a given month for the specified study. To display the Visits Due listing, go to the LISTINGS menu screen and select *Visits due*. Key the study number, month (as a 2 digit number, e.g. **04** for April) and year (as a 4 digit number, e.g. **2011**) of interest and click on *Submit*.

A list of all participants with a target visit date in the month and year selected is generated as in figure 9.12a. The list also includes the visit window dates.

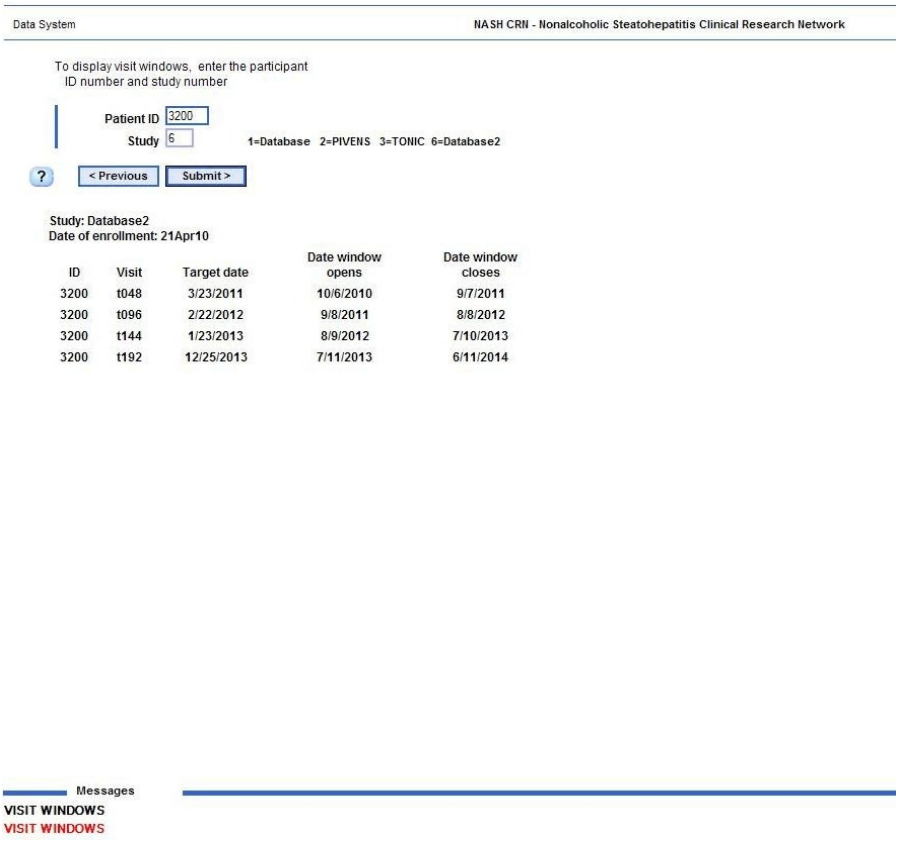
9.12a Visits Due listing (figure)



9.13. Visit Windows listing

The Visit Windows option will display a list of all visit window dates for a given participant in the specified study as in figure 9.13a below. The list includes the target, window open, and window close dates by visit code for all follow-up visits. To produce the Visit Windows listing by participant, go to the LISTINGS menu screen and select *Visit windows*. Key the patient ID and the study number, then click *Submit*.

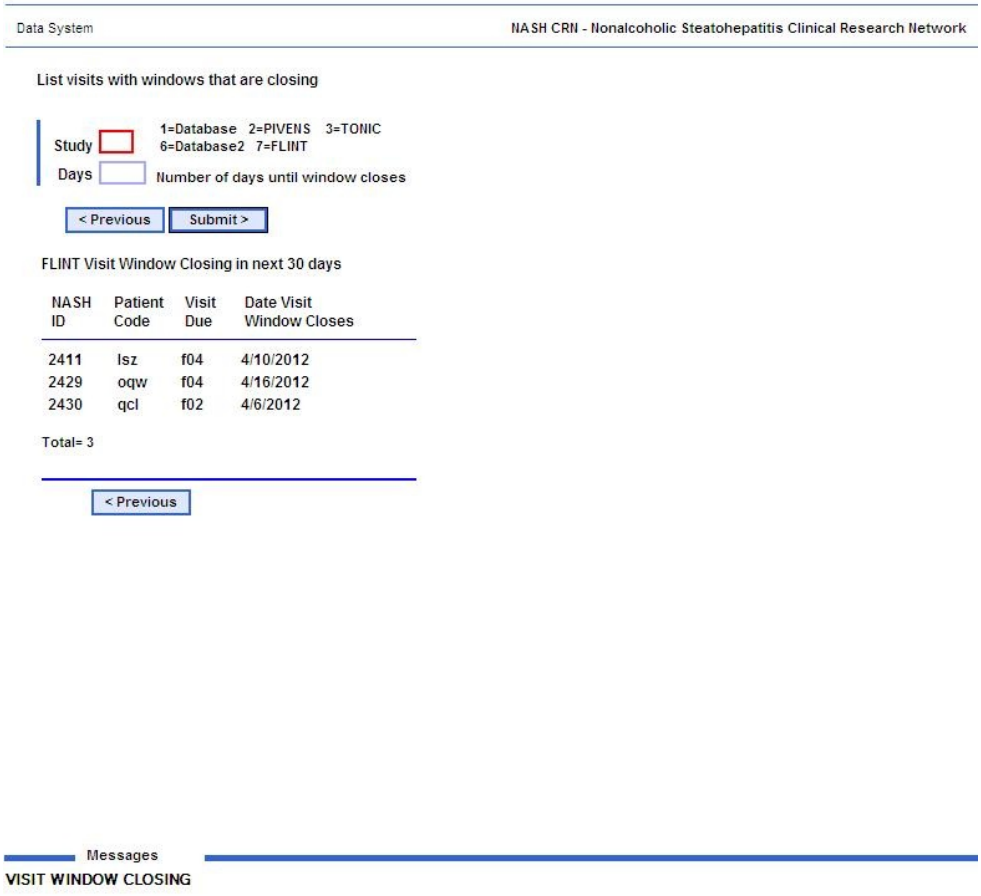
9.13a Visit Windows listing (figure)



9.14. Visit Window Closings listing

The Visit Window Closings option displays a list of visits that will close in a user-defined time period for a specified study. To display the Visit Window Closings listing as in figure 9.14a, go to the LISTINGS menu. Click on *Visit window closings*. Key the study number and the number of days until the window closes, then click *Submit*. This is helpful if you need to know what visits will be closing soon.

9.14a Visit Window Closings listing (figure)



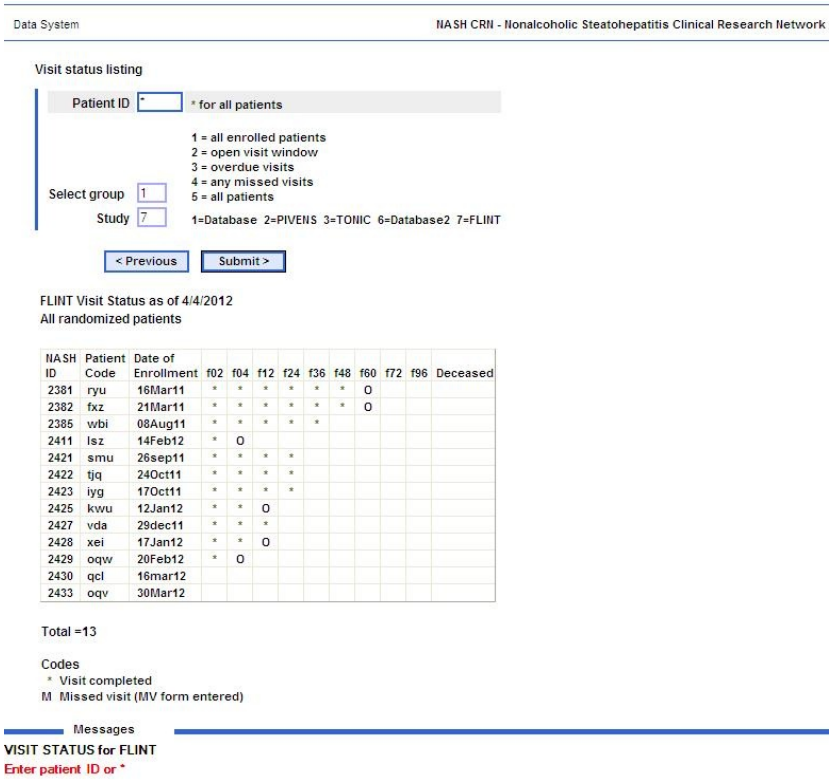
9.15. Visit Status Report

The Visit Status Report option displays a list of the current study status for either a participant or a group of participants for a specified study. The codes used are:

- * = Visit completed
- M = Missed visit (MV form entered)
- O = Open Visit window
- X = Overdue visit (window is closed but no forms are keyed)
- I = Incomplete visit (MV form with some other visit forms are keyed)

To display the Visit Status Report listing in figure 9.15a, go to the LISTINGS menu. Click on *Visit Status*. For a specified participant, key the Patient ID. For a group of participants, key an asterisk **(*)** in the Patient ID and a group code (**1**= all enrolled participants, **2**=open visit window, **3**=overdue visits, **4**=any missed visits), enter the study number, then click *Submit*.

9.15a Visit Status Report listing (figure)

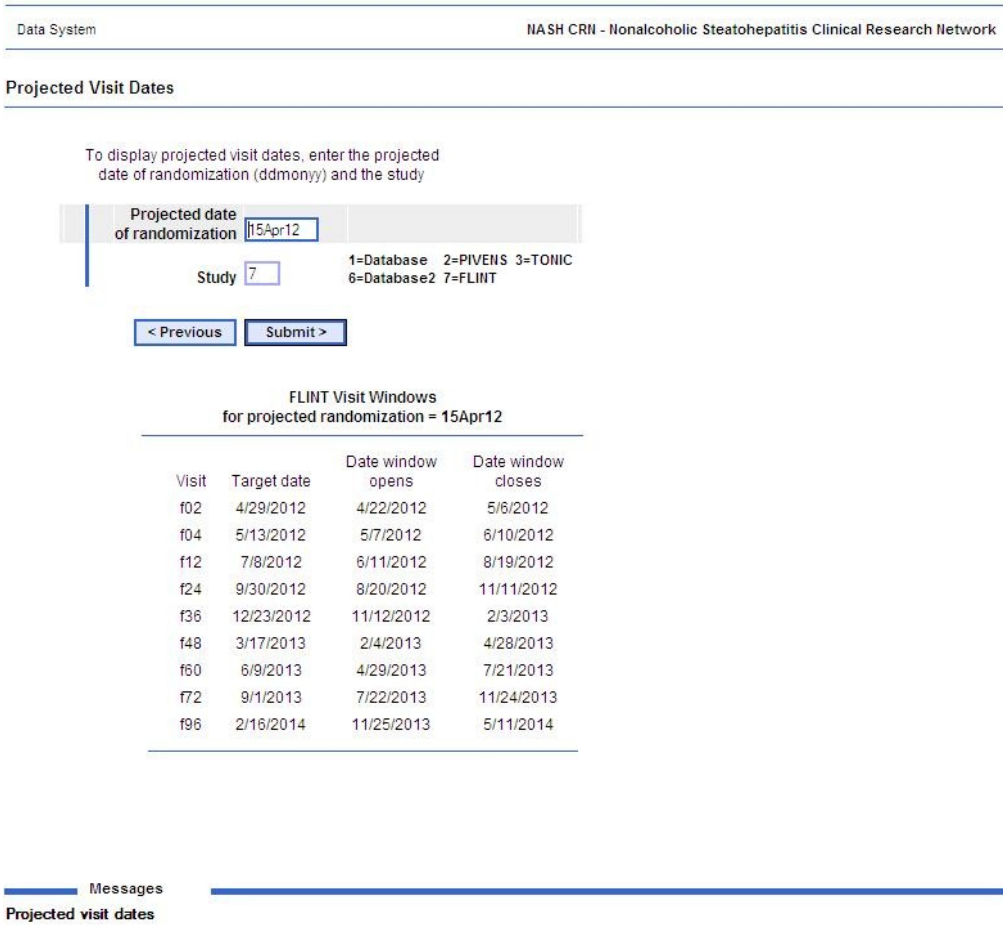


9.16. Projected Visits report

The Projected Visits report lists the projected visit window schedule for a given enrollment/randomization date for a specified study. This can be helpful if a participant needs to know what his visit schedule would be if s/he were enrolled in the study on a given date.

To display the Projected Visits report, go to the LISTINGS menu, select *Projected visits*, key the projected randomization date into a NASH CRN treatment trial and the study number, then click *Submit*.

9.16a Projected Visit Dates listing (figure)



Data System — NASH CRN - Nonalcoholic Steatohepatitis Clinical Research Network

Projected Visit Dates

To display projected visit dates, enter the projected date of randomization (ddmonyy) and the study

Projected date of randomization: 15Apr12

Study: 7 (1=Database 2=PIVENS 3=TONIC 6=Database2 7=FLINT)

< Previous | Submit >

FLINT Visit Windows
for projected randomization = 15Apr12

Visit	Target date	Date window opens	Date window closes
f02	4/29/2012	4/22/2012	5/6/2012
f04	5/13/2012	5/7/2012	6/10/2012
f12	7/8/2012	6/11/2012	8/19/2012
f24	9/30/2012	8/20/2012	11/11/2012
f36	12/23/2012	11/12/2012	2/3/2013
f48	3/17/2013	2/4/2013	4/28/2013
f60	6/9/2013	4/29/2013	7/21/2013
f72	9/1/2013	7/22/2013	11/24/2013
f96	2/16/2014	11/25/2013	5/11/2014

Messages

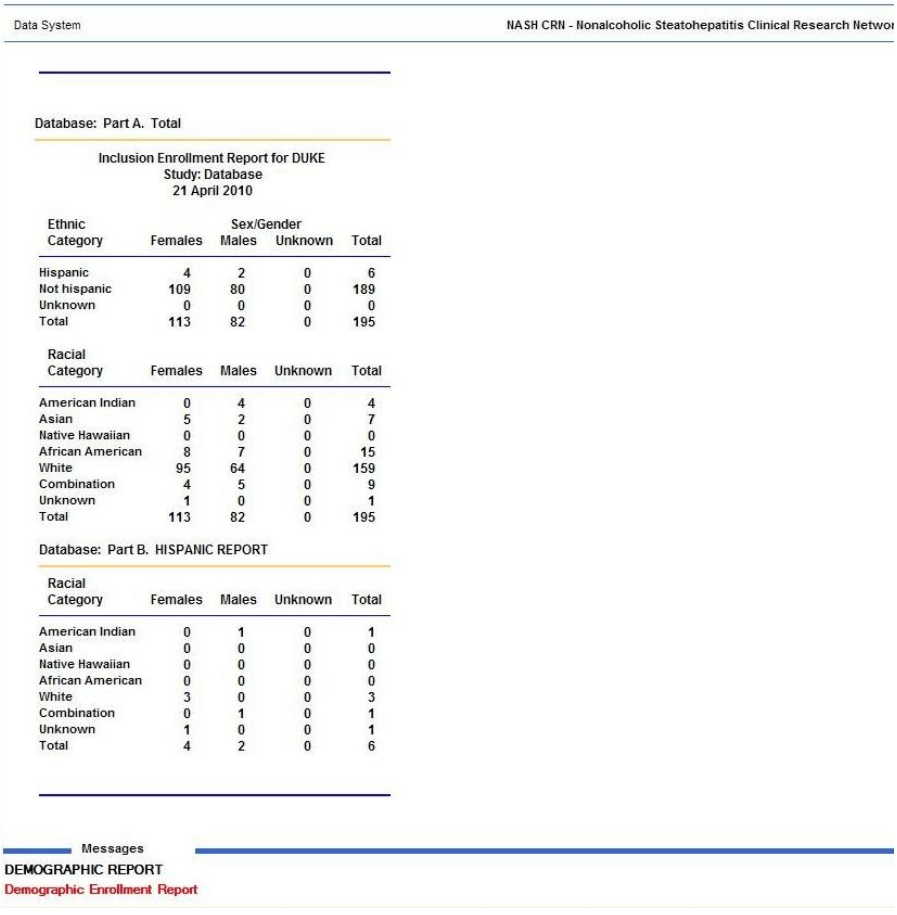
Projected visit dates

9.17. Clinic Demographics Report

The Clinic Demographics Report displays the demographic (sex/gender and ethnic or racial category) tables by study for all participants enrolled or randomized into each study at your clinic as in figure 9.17a below.

To generate your clinic's demographic report, go to the LISTINGS menu and click on *Clinic demographics*.

9.17a Clinic demographics report (figure)



Data System — NASH CRN - Nonalcoholic Steatohepatitis Clinical Research Networ

Database: Part A. Total

Inclusion Enrollment Report for DUKE
Study: Database
21 April 2010

Ethnic Category	Sex/Gender Females	Males	Unknown	Total
Hispanic	4	2	0	6
Not hispanic	109	80	0	189
Unknown	0	0	0	0
Total	113	82	0	195

Racial Category	Females	Males	Unknown	Total
American Indian	0	4	0	4
Asian	5	2	0	7
Native Hawaiian	0	0	0	0
African American	8	7	0	15
White	95	64	0	159
Combination	4	5	0	9
Unknown	1	0	0	1
Total	113	82	0	195

Database: Part B. HISPANIC REPORT

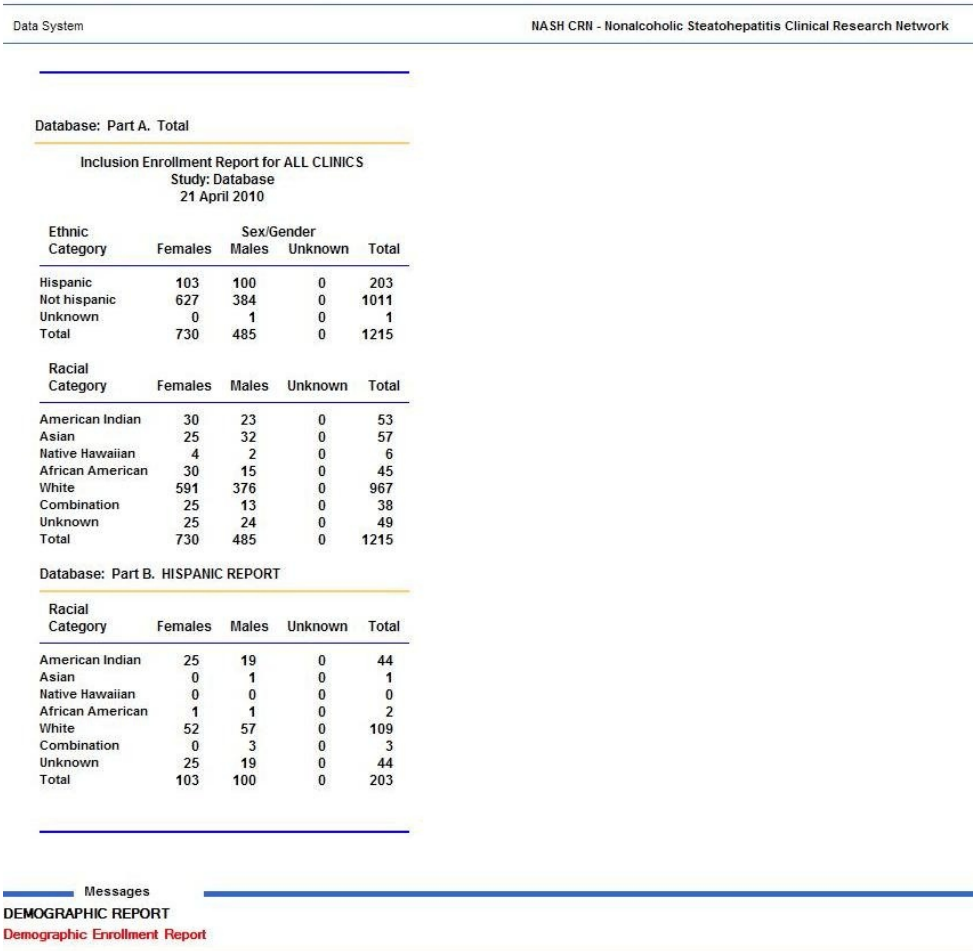
Racial Category	Females	Males	Unknown	Total
American Indian	0	1	0	1
Asian	0	0	0	0
Native Hawaiian	0	0	0	0
African American	0	0	0	0
White	3	0	0	3
Combination	0	1	0	1
Unknown	1	0	0	1
Total	4	2	0	6

Messages
DEMOGRAPHIC REPORT
Demographic Enrollment Report

9.18. Demographics report

The Demographics report displays study-specific demographic tables for the enrolled or randomized participants by ethnicity and gender for all of the clinics combined as in figure 9.18a below. To generate the combined clinics' demographics report, go to the LISTINGS menu and select *Total demographics.* This generates total demographics tables for each study in the NASH CRN. Scroll down until you find the study demographics that you need.

9.18a Demographics report (figure)



Data System — NASH CRN - Nonalcoholic Steatohepatitis Clinical Research Network

Database: Part A. Total

Inclusion Enrollment Report for ALL CLINICS
Study: Database
21 April 2010

Ethnic Category	Sex/Gender Females	Males	Unknown	Total
Hispanic	103	100	0	203
Not hispanic	627	384	0	1011
Unknown	0	1	0	1
Total	730	485	0	1215

Racial Category	Females	Males	Unknown	Total
American Indian	30	23	0	53
Asian	25	32	0	57
Native Hawaiian	4	2	0	6
African American	30	15	0	45
White	591	376	0	967
Combination	25	13	0	38
Unknown	25	24	0	49
Total	730	485	0	1215

Database: Part B. HISPANIC REPORT

Racial Category	Females	Males	Unknown	Total
American Indian	25	19	0	44
Asian	0	1	0	1
Native Hawaiian	0	0	0	0
African American	1	1	0	2
White	52	57	0	109
Combination	0	3	0	3
Unknown	25	19	0	44
Total	103	100	0	203

Messages
DEMOGRAPHIC REPORT
Demographic Enrollment Report

10. Audit procedures

Purpose:

- To check the completeness and accuracy of data entered into the electronic database

When:

- Periodically (approximately monthly) as requested by the DCC

Procedures:

1. The DCC will e-mail the clinics a list of forms to be audited.
2. Within 14 business days of receiving the list from the DCC, the clinic will mail (via Fed Ex or trackable delivery) or scan and email copies of these forms to the DCC for review. Clinics are **not** to fax forms. Any participant identifying information, e.g., patient's name on copies of lab results, must be blacked out.
3. The DCC will review these forms by comparing the data on the paper form with the data entered in the electronic database.
4. The DCC will return audit results in a Clinic Audit Report memo via e-mail. This report will summarize the discrepancies.
5. If necessary, the clinic will use the CHANGE function of the data entry system to edit (correct or complete) the data in the database in response to the Clinic Audit Report.
6. The clinic will return the Clinic Audit Report memo describing their actions to the DCC by fax. The response to each audit should be hand-written on the audit memo.
7. Discrepancy rates will be calculated and clinics' discrepancy rates will be compared in performance report tables produced monthly by the DCC and for DSMB and Steering Committee meetings.

11. Appendices

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Appendix 11.1. Clinic ID codes, Patient IDs, and RTI numbers

Clinic	Clinic ID	Patient IDs	Site ID number
Case Western Reserve University	CWRU	1001-1999	220
○ Cleveland Clinic Foundation	CCF		
○ Cincinnati Children's Hospital	CINC		
Columbia University	CU	9101-9999	828
Duke University	DUKE	2001-2999	222
○ Children's Memorial Hospital	NWU		
○ Johns Hopkins University	JHU		
Indiana University	IU	3001-3999	221
Saint Louis University	SLU	4001-4999	223
○ Texas Children's Hospital (Baylor)	BCM		
University of California, San Diego	UCSD	5001-5999	224
University of California, San Francisco	UCSF	6001-6999	225
○ California Pacific Medical Center	CPMC		
Virginia Mason Medical Center	VMMC	7001-7999	226
○ Seattle Children's Hospital	UW		
Virginia Commonwealth University	VCU	8001-8999	227
○ Mount Sinai Kravis Children's Hospital	MSCH		
○ Emory University	EU	(8721-8300)	

Site ID numbers to be used in specimen banking at the Biosample Repository (Fisher) and Genetics Repository (Rutgers Univ.) Site ID numbers assigned by RTI International for the NIDDK Data Repository.

Appendix 11.2. Forms for use with the tutorial

To complete the tutorial, 10 completed forms for the Database study for visit S1 for a dummy participant (patient ID = 9055, patient code = aha) must be entered. Print these forms from the NASH CRN website: http://jhuccs1.us.com/nash/closed/docs/sop/database/tutorialforms.pdf; the tutorial forms can also be accessed from the SOP web page for any of the current NASH CRN studies.

These forms are for use with the tutorial **only**. The Clinic ID is left blank on the forms; your center's Clinic ID code will automatically be generated by the data system according to the log-on Clinic ID. The forms you will enter are:

- RG0 - Registration
- HF0 - Liver Biopsy Histology findings
- LR0 - Laboratory Results
- LQ0 - Symptoms of Liver Disease
- AD0 - AUDIT
- LS0 - Laboratory Results - Tests Done only During Screening
- IR0 - Liver Imagining Studies
- PA0 - Physical Activity
- PE0 - Physical Examination
- ED0 - Registry Enrollment

Note that these form versions are NOT the same as the data entry forms used to key actual study participants.

Appendix 11.3. Rules for data entry

Type of item	Rule	Other notes
All items	• Completely fill the data entry space • Key EXACTLY what is written • After keying, press ENTER (initiates system data checks) or click in next item to be entered	• EXCEPTIONS to filling all of the space are: Letter codes: alpha Center ID, visit code Special response codes Other (*specify*) field General comments fields • System edit error message appears if a required data item is left blank
Signatures	If present, key **1**	If not present, key **?**
Letter	• Left-adjust • Trailing spaces left blank	• Examples are password, Name Code, Center ID, Visit Code • Stored as lowercase in database
Numeric	• Key leading and trailing zeros • Do NOT key decimals or commas	Example of a numeric item format _ _ • _ : Actual response value = 1.0 Form recorded value = 0 1 • 0 Keyed value = 010
Date	• Completely fill the data entry space • Key EXACTLY what is written	• All dates formatted as ddmmmyy where yy=2-digit year. Birthdates require a 4-digit year.
Check all that apply	• If item checked, key **1** • If not checked, leave blank	**CAUTION:** Make sure either **ENTER** is pressed after each possible response OR click in each field checked.
Other, (*specify*)	• Key EXACTLY as written • Up to 35 characters are allowed • Not case-sensitive	• If response > 35 characters, key excess response in General Comments field • Do NOT use a question mark (**?**) or an ampersand (&) or plus sign (+) or equal sign (=) or asterisk (*) or quotes (“ or ’) in a response • All characters are automatically converted to lower case in the data system

Appendix 11.3. Rules for data entry

Type of item	Rule	Other notes
General Comments	• 5 lines available • Up to 75 characters are allowed per line • Case-sensitive	• Final screen for each form • Do NOT use a question mark (**?**), ampersand (&), plus sign (+), equal sign (=), asterisk (*), quotes (“ or ’) in a response • Generally, not a required data item field • An explanation keyed in the General Comments is required for any items coded with a **r** (refuse) or **m** (missing) code. A DCC edit report error will be generated for any such item missing an explanation.
Special response codes	**d** = don’t know **n** = not applicable **r** = refused **s** = too sick to provide data **m** = missing **m m year** = missing date field (either the month and/or day missing) **?** = query: temporarily missing	• Data entry technician should key what is written on the form, not infer code • EXCEPTION is the data entry technician may need to key the query code (a question mark,**?**) if the data item is temporarily missing or illegible, in order to save the form data • Key 1 character code for any size field • Left-adjusted • See Appendices 11.4 and 11.5 for detailed use of codes

Appendix 11.4. Special data entry codes

CODE	DEFN	WHEN USED	INSTRUCTIONS*	IN DCC EDIT/Audit REPORT**
r	refuse	Participant refuses to answer the question or refuses to perform the procedure or test.	• Write a brief explanation on the form indicating the reason for refusal of the procedure or to respond to the form questions or that the participant did not provide a reason. • Make sure the reason is also data entered in General Comments. • If the participant refuses to answer just a few questions, a refusal reason is not required, but helpful if the information is available.	If the data form is audited and a note of explanation is missing from the form and/or database, the item will be noted in the audit report.
d	don't know	Participant says he/she does not know the answer.		Edit messages will not be sent regarding **d** codes.
n	not applicable	The item is not applicable.		Edit messages will not be sent regarding **n** codes.
s	too sick to provide data			Edit messages will not be sent regarding **s** codes.
m	missing	• The information requested is missing or permanently not available. • If information is missing but WILL become available, then code **?**.	• Write a brief explanation on the form indicating the reason why the information is missing. • Make sure that the data system operator keys the note.	An edit message will be sent for each **m** code without a note in the database regarding why the item is missing. The purpose of the edit message is to verify that the information is truly missing.
m m year	partial missing date	The year of the date is known, but the day and/or month is missing.	• When the entire date is missing, use a single **m** to designate that the entire field is missing. • Otherwise use an **m** within the date to designate the missing month and/or day: (e.g. **m oct06** or **m m 06**).	Edit messages will not be sent regarding partial date codes.

*Write one special code character in the space for the response even if the response space allows for more than one character (i.e., write **r** or **m**, NOT **rr** or **mmm**) and then press ENTER.

**If there are any questions about edits or an edit message is repeated despite having previously been responded to, fax the DCC a copy of the original edit sheet and the sheet with the repeat edit, together with a note describing the problem. The DCC will investigate it and correct the problem or give instructions on how to correct the problem.

Appendix 11.5. Use of ? (query) as data entry code

The data entry code for an item with an outstanding query is the question mark symbol, **?**. This code should be used when data are temporarily missing (e.g., if handwriting cannot be deciphered and the person completing the form is not immediately available, or if lab results have not been received yet by the clinic).

Form items keyed as **?** need to be edited (i.e., the **?** item in the form needs to be resolved eventually once the data is available). All items coded with a **?** will be listed in batch edit sheets prepared by the DCC until the **?** is replaced with a response or other data entry code.

Please note that use of a question mark symbol (?) in a comment or specify item will result in an edit message. Instead of keying a question mark in these items, indicate uncertainty in a response by keying "possibly", "quest", "maybe", etc.

Once the missing data item is available and the hard copy form has been updated and initialed, the electronic form record must be edited. To edit data, select *Data Entry* on the MAIN TASKS menu. Click *Change a data form* on the DATA ENTRY action menu to access previously keyed forms in CHANGE mode (see section 7.3).

Forms with edits or outstanding queries will be listed in the batch edit sheets prepared by the DCC until resolved, or they can be listed by the clinic using the *Listings* task on the MAIN TASKS menu and clicking on *?s* to display the Outstanding Queries report (see section 9.7).

Note that a participant cannot be enrolled or randomized in a study if any items are keyed as ? in the baseline data. All baseline data must be obtained prior to enrollment in a study.

Appendix 11.6. Resolution of data system error message

When occurs	Type of error message	Error resolution
Data entry error	• Keyed value is not in correct format, or within the allowable range • Required item is left blank • Item keyed that should be skipped	• Keyed value is not same as the form response ▸ key the correct value • Keyed value is same as the form response ▸ key the correct format, e.g. - do NOT key a decimal point - key leading and trailing zeroes - key correct date format (ddmmmyy) where mmm is alphabetic - if the "Other" response is checked, then *specify* should contain a response - PIN numbers and a **1** for the study physician or clinical coordinator signature must be keyed (if signature is present) or **?** is signature is absent • Make sure that response to "Check all that apply" is indicated at the correct line • If value is not within the available range and is verified to be correct, then contact DCC.
Data entry error	• Value is inconsistent with another item in the 1st keying; example is date keyed for the "date form reviewed" is earlier than the "Visit date" recorded	• One of the 2 items is not the same as the responses written on the form or the form was not completed correctly. • Key the correct value or a **?**
Data entry error	• Inconsistency between 2 keyings **NOTE**: The value for the 1st keying will be displayed in the error message.	• Compare keyed responses and written form response and check formats • If 1st keying is correct ▸ key correct value ▸ press ENTER • If 2nd keying is correct ▸ press ENTER

Appendix 11.6. Resolution of data system error message

When occurs	Type of error message	Error resolution
Keyed item agrees with the response on the written data form, and that response is determined to be incorrect.	• A required item was left blank • An item was filled in that should have been skipped • A response was coded to an out of range value • Measurement units are coded, but the value is inconsistent with the specified scale • No signatures • A checked "Other" response does not have a *specify* response	• Flag temporarily (e.g. with a post-it tab) the invalid or inconsistent response on the form • IF clinical coordinator is available ▸ have them correct the form ▸ key the correct response. • IF the coordinator is not available ▸ key a question mark (**?**) in order to complete data entry and save the record • NOTE: The data entry technician should NEVER change the form data and should only key corrected data that has been verified, corrected, and initialed with an explanation written on the form by an authorized person.
No error is found either in data entry or on the written form	Could be any of the error messages listed above	• Write down the error message and print screen • Key the query code (**?**) • Contact the DCC • May require a change in the data system checks - e.g., value ranges may need to be expanded
Within the data system	Data system or script error	• Write down the error message and print screen • Exit the data system • Contact the DCC • Once resolved, data system activities may resume

Keyed: ( )

NAFLD Database

RG - Registration

DRAFT

Purpose: To register patients as candidates for enrollment in NAFLD Database and to assign a patient ID number. This is the first form completed for a NAFLD Database patient. The Registration Form must be the first form keyed, before any other NAFLD Database forms. Patients should not be registered prior to being seen at visit s1.

When: At first screening visit (s1).

Administered by: Clinical Coordinator.

Respondent: Patient and parent (if patient is age 17 or younger).

Instructions: Use Flash Cards as instructed. Do not assign an ID if patient has previously been assigned an ID for a NASH CRN study.

A. Center, patient and visit identification

1. Center ID: ____ ____ ____ ____

2. Patient ID: 9055

3. Patient code: AHA

4. Visit date: 25 MAY 04 (day mon year)

5. Visit code: s1

6. Form & revision: rg0

7. Study: NAFLD Database 1

B. Consent

8. After reviewing the existing records (e.g., liver biopsy, imaging studies, elevated aminotransferases and/or history) does the Study Physician feel that the patient may be suitable for the NAFLD Database:

   (✓1) Yes (2) No → STOP

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

   (✓1) Yes (2) No → STOP

C. Information about patient

10. Date of birth: 29 JAN 1952 (day month year)

Record 4-digit year for date of birth.

11. Age at last birthday: 52 years

12. Gender:

    Male (✓1)
    Female (2)

13. Ethnic category *(show the patient/parent 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) → 15.

14. What describes your Hispanic, Latino, or Latina origin best *(show the patient/parent Flash Card #1 and ask the respondent to pick the subcategory that best describes their 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

15. Racial category *(show the patient/parent 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/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)

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

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

_____
specify

17. Highest educational level achieved by patient *(show the patient/parent Flash Card #3 and ask the respondent to pick the category that describes the patient best; check only one):*

- Never attended school (0)
- Kindergarten, pre kindergarten, or younger (1)
- Grades 1 to 5 (2)
- Grades 6-8 (3)
- Grades 9-11 (4)
- Completed high school (5)
- Some college or post high school education or training (6)
- Bachelor's degree or higher (✓7)

18. Is the patient currently employed:

Yes (✓1) No (2)

21.

19. What is the patient's current occupation:

Contractor
specify occupation

20. About how many hours does the patient work each week: 45
hours

21. Which of the following categories best characterizes the patient's occupational history *(show the patient/parent Flash Card #4 and ask the respondent to pick the category that describes the patient best; check only one):*

- Never employed (0)
- Laborer (1)
- Clerical (2)
- Professional (✓3)
- Homemaker (4)
- Other, *(specify):* (5)

_____
specify

22. Marital status of the patient *(show the patient/parent Flash Card #5 and ask the respondent to pick the category that describes the patient best; check only one):*

- Single, never married (1)
- Married or living in marriage-like relationship (✓2)
- Separated, divorced, or annulled (3)
- Widowed (4)

23. Combined annual income before taxes of all members of patient's household *(show the patient/parent Flash Card #6 and ask the 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)

24. Is the patient under age 18:

Yes (1) No (✓2)

29.

25. Current age of patient's mother, stepmother, or female guardian *(show patient/parent Flash Card #7; check only one):*

- Not applicable (mother is deceased or patient has no stepmother or female guardian) (1)
- 19 or younger (2)
- 20-29 years (3)
- 30-39 years (4)
- 40-49 years (5)
- 50-59 years (6)
- 60 years or older (7)

26. Highest educational level achieved by patient's mother, stepmother, or female guardian *(show patient/parent Flash Card #8; 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)

27. Current age of patient's father, stepfather, or male guardian *(show patient/parent Flash Card #7; check only one):*

Not applicable (father is deceased or patient has no stepfather or male guardian)	(1)
19 or younger	(2)
20-29 years	(3)
30-39 years	(4)
40-49 years	(5)
50-59 years	(6)
60 years or older	(7)

28. Highest educational level achieved by patient's father, stepfather, or male guardian *(show patient/parent Flash Card #8; 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)

D. Source of patient

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

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

HMO-based	(01)
Primary care clinic	(✓02)
Internal medicine clinic	(03)
Pediatric clinic	(04)
Pediatric weight disorders clinic	(05)
GI liver clinic	(06)
Liver transplant clinic	(07)
Obesity clinic	(08)
Bariatric surgery clinic	(09)
Diabetes clinic	(10)
Lipid disorders clinic	(11)

E. Previous registration in a NASH CRN study

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

Yes (1) No (✓2)

34.

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

a. PIVENS:	(1)
b. TONIC:	(1)
c. Other, *(specify):*	(1)

_____

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

____ ____ ____ ____

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

____ ____ ____

35.

F. ID assignment

(If a STOP 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.)

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

9055 ####
aha zzz

G. Administrative information

35. Clinical Coordinator PIN: 903

36. Clinical Coordinator signature: Cindy Coordinator

37. Date form reviewed: 26 MAY 04
day mon year

Keyed: ( )

NAFLD Database

LR - Laboratory Results - Tests Done During Screening and Followup

DRAFT

Purpose: To record archival and current laboratory test results for tests done during both screening and followup.
When: Visits s1, f048, f096, f144, and f192.
Administered by: Study Physician (adult hepatologist or pediatrician) and Clinical Coordinator.
Instructions: Laboratory test results may be obtained from chart review. Complete tests as needed (repeat test if archival test is not within the required time window). The window for each test is specified next to the date of blood draw.

A. Center, patient, and visit identification

1. Center ID: ____
2. Patient ID: 9055
3. Patient code: AHA
4. Date of visit *(date form was initiated)*: 27 MAY 04 (day / mon / year)
5. Visit code: S1
6. Form & revision: 1 r 0
7. Study: NAFLD Database 1

B. Hematology

8. Date of blood draw for complete blood count: 25 MAY 04 (day / mon / year)
   Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database appointment schedule).
9. Hemoglobin: 17.5 g/dL
10. Hematocrit: 42.0 %
11. White blood cell count (WBC): 12,500 cells/ µL
12. Platelet count: 350,000 cells/ µL

C. Chemistries

13. Date of blood draw for chemistries: 25 MAY 04 (day / mon / year)
    Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database appointment schedule).
14. Sodium: 138 mEq/L
15. Potassium: 05.4 mEq/L
16. Chloride: 107 mEq/L
17. Bicarbonate: 28.0 mEq/L
18. Calcium: 07.4 mg/dL
19. Phosphate: 05.3 mg/dL
20. Blood urea nitrogen (BUN): 18 mg/dL
21. Creatinine: 00.9 mg/dL
22. Uric acid: 04.4 mg/dL
23. Total protein: 08.6 g/dL
24. Date of blood draw for HbA1c: 28 APR 04 (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 Database appointment schedule).
25. HbA1c: 07.6 %

Patient ID: 9055

D. Liver panel

26. Date of blood draw for liver chemistries: 25 (day) MAY (mon) 04 (year)

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database appointment schedule).

27. Bilirubin (total): 02.8 mg/dL

28. Aspartate aminotransferase (AST) 280 U/L

a. Upper limit of normal: 060 U/L

b. Lower limit of normal: 015 U/L

29. Alanine aminotransferase (ALT) 048 U/L

a. Upper limit of normal: 035 U/L

b. Lower limit of normal: 000 U/L

30. Alkaline phosphatase 220 U/L

a. Upper limit of normal: 130 U/L

b. Lower limit of normal: 040 U/L

31. Gamma glutamyl transferase (GGT): 061 U/L

32. Albumin: 4.3 g/dL

33. Globulin: 5.4 g/dL

34. Prothrombin time (PT): 22 sec

35. International normalized ratio (INR): 0.9

E. Fasting lipid profile

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

36. Date of blood draw for fasting lipid profile: 25 (day) MAY (mon) 04 (year)

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database appointment schedule).

a. Triglycerides: 154 mg/dL

b. Total cholesterol: 235 mg/dL

c. HDL cholesterol: 057 mg/dL

d. LDL cholesterol: 115 mg/dL

F. Fasting glucose and insulin

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

37. Date of blood draw for fasting plasma glucose and insulin levels: 05 (day) MAY (mon) 04 (year)

Date must be within the required time window: within 6 months of screening or in the time window for the followup visit (check the patient's Database appointment schedule).

a. Glucose: 075 mg/dL

b. Insulin: 021.5 mu/mL

G. Administrative information

38. Study Physician PIN: 910

39. Study Physician signature: Neville Nash

40. Clinical Coordinator PIN: 903

41. Clinical Coordinator signature: Cindy Coordinator

42. Date form reviewed: 01 (day) JUN (mon) 04 (year)

NAFLD Database

HF - Liver Biopsy Histology Findings

DRAFT

Purpose: Record results of pathology evaluation of slides from liver biopsy.
When: Baseline and during followup as needed (visits s1, f024, f048, f096, f144, or f192).
By whom: Study Pathologist at the NASH CRN clinical center (this is not the form used for central reading) and Clinical Coordinator.
Instructions: Upon completion of this form, the Pathologist should give the original HF form to the Clinical Coordinator. If the biopsy was adequate for scoring, the Pathologist should send the slides to the Clinical Coordinator for forwarding to the Histology Review Center.

A. Center, patient and visit identification

1. Center ID: ____
2. Patient ID: 9055
3. Patient code: AHA
4. Date of visit *(date form was initiated)*: 04 (day) JUN (mon) 04 (year)
5. Visit code: s1
6. Form & revision: hf0
7. Study: NAFLD Database 1

B. Biopsy information

8. Date this biopsy was performed: 15 (day) APR (mon) 04 (year)
9. Local surgical pathology accession number *(e.g., specimen ID number)*: 04-82697 (accession number)
10. What pathology laboratory did this biopsy come from:
    - NASH CRN clinical center's lab (✓1) → 11.
    - Other *(specify)*: (2)

    name of lab

    address of lab

    address of lab
11. Biopsy length (mm): 12 mm
12. Number of slides given to NASH CRN clinical center for evaluation:
    - a. H & E: 02
    - b. Trichrome: 02
    - c. Unstained: 10

C. NAFLD/NASH evaluation

13. Date of reading: 01 (day) JUN (mon) 04 (year)
14. Is the biopsy adequate for scoring purposes:
    Yes (✓1) No (* 2) → 28.

    ** Return the slides to original pathology laboratory.*
15. Steatosis *(assume macro, e.g., large and small droplet)*
    - a. Grade:
      - < 5% (0)
      - 5-33% (✓1)
      - 34-66% (2)
      - > 66% (3)
    - b. Location:
      - Zone 3 (0)
      - Zone 1 (✓1)
      - Azonal (2)
      - Panacinar (3)

16. Fibrosis stage *(Masson's trichrome stain)*

- None (0)
- Mild, zone 3, perisinusoidal (requires trichome) (1)
- Moderate, zone 3, perisinusoidal (easily seen on H&E) (✓2)
- Portal/periportal only (3)
- Zone 3 and periportal, any combination (4)
- Bridging (5)
- Cirrhosis (6)

17. Inflammation

a. Amount of lobular inflammation: combines mononuclear, fat granulomas, and pmn foci:

- 0 (0)
- < 2 under 20x mag (1)
- 2-4 under 20x mag (✓2)
- > 4 under 20x mag (3)

b. Amount of portal, chronic inflammation:

- None (0)
- Mild (✓1)
- Greater than mild (2)

18. Ballooning:

- None (0)
- Few (✓1)
- Many (2)

19. Is steatohepatitis present:

- No (1)
- Suspicious/borderline/indeterminate (✓2)
- Yes, definite (3)

D. Exclusion of other liver disease

20. Is there evidence of primary biliary cirrhosis:

Yes (1) No (✓2)

21. Is there evidence of Wilson's disease:

Yes (1) No (✓2)

22. Features of chronic cholestatic liver disease *(check all that apply)*

- **a.** Bile duct loss/infiltration/sclerosis: (1)
- **b.** Florid duct lesions: (1)
- **c.** Cholate stasis: (1)
- **d.** Copper deposition: (1)
- **e.** Other *(specify):* (1)

_____

- **f.** None: (✓1)

23. Features of other forms of chronic liver disease *(check all that apply)*

- **a.** Vascular lesions of ALD/B-C/OVD: (1)
- **b.** Inflammation suggestive of AIH, HCV: (1)
- **c.** Pigment suggestive of HH: (1)
- **d.** Globules suggestive of A1AT: (1)
- **e.** Hepatocellular changes suggestive of HBV: (1)
- **f.** Granulomas suggestive of sarcoid, PBC, infection: (1)
- **g.** Other *(specify):* (1)

_____

- **h.** None: (✓1)

24. Features to suggest pre-existing steatohepatitis *(check all that apply)*

- **a.** Mallory's hyaline (r/o cholate stasis): (1)
- **b.** Perisinusoidal fibrosis away from septa: (1)
- **c.** Hepatocyte ballooning: (1)
- **d.** Megamitochondria: (1)
- **e.** Other *(specify):* (1)

_____

- **f.** None: (✓1)

E. Evaluation of cryptogenic cirrhosis

25. Is cirrhosis present:

( ) Yes (1) (✓) No (2)

→ 27.

26. In your opinion, is this **cryptogenic cirrhosis**
(cirrhosis that fails to meet criteria for NAFL and without evidence of other form(s) of chronic liver disease):

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

F. Other comments

27. Other comments:

_____

_____

_____

_____

_____

G. Administrative information

28. Study Pathologist PIN: 936

29. Study Pathologist signature: Barry Biopsy

30. Clinical Coordinator PIN: 903

31. Clinical Coordinator signature: Cindy Coordinator

32. Date form reviewed: 08 - JUN - 04
day mon year

LQ – Symptoms of Liver Disease

Keyed: ( )
DRAFT

Purpose: To obtain the patient's view of his/her liver disease symptoms.
When: Visits s1, f048, f096, f144, and f192.
Administered by: Self-administered during the visit, but Clinical Coordinator must be available to answer questions and review for completeness.
Respondent: Patient, 18 years of age or older.
Instructions: The Clinical Coordinator should complete Part A below and attach a label to each of pages 2-4. The patient should complete pages 2-4 during the visit. 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: 9055
3. Patient code: AHA
4. Date of visit: 04 - JUN - 04 (day - mon - year)
5. Visit code: S1
6. Form & revision: 1q0
7. Study: NAFLD Database 1

B. Administrative information

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

8. Clinical Coordinator
   a. PIN: 903
   b. Signature: Cindy Coordinator
9. Date form reviewed: 07 - JUN - 04 (day - mon - year)

Affix label here

Patient ID: 9055
Patient code: AHA
Visit code: S1

Symptoms of Liver Disease

Instructions: People with liver disease may or may not have symptoms, such as pain over the liver area (right upper quadrant), nausea, poor appetite, itching, tiredness, or fatigue. In this questionnaire, we are trying to identify what symptoms you have, how severe they are, and how much they affect your life style.

(Items 1-9 are reserved for clinical center use.)

10. 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**	**Moderately**	**Quite a bit**	**Extremely**
a. Pain over liver (right upper quadrant)	1	2	(3)	4	5
b. Nausea	1	(2)	3	4	5
c. Poor appetite	1	(2)	3	4	5
d. Weight loss	(1)	2	3	4	5
e. Diarrhea	(1)	2	3	4	5
f. Muscle aches (eg, cramps)	1	2	(3)	4	5
g. Muscle weakness	1	(2)	3	4	5
h. Headaches	1	2	3	(4)	5
i. Easy bruising	1	(2)	3	4	5
j. Itching	(1)	2	3	4	5
k. Irritability	1	2	(3)	4	5
l. Depression/sadness	1	(2)	3	4	5
m. Trouble sleeping	1	2	3	(4)	5
n. Trouble concentrating	1	(2)	3	4	5
o. Jaundice (yellow color to skin, eyes, etc)	(1)	2	3	4	5
p. Dark urine	(1)	2	3	4	5
q. Swelling of ankles	(1)	2	3	4	5
r. Swelling of abdomen	1	2	(3)	4	5

Affix label here

Patient ID: 9055
Patient code: AHA
Visit code: S1

11. Which of the following best describes your level of fatigue and the effects of your fatigue *(choose only one)*:

Circle one

I feel completely normal and have no fatigue **(circle the number 1 to the right and stop; you do not need to answer any more of the questions - thank you for filling out the questionnaire)** 1
I have some fatigue, but I can do what I want to do without difficulty ... (2)
I have fatigue, and I do what I want to do but with difficulty 3
I have fatigue and it keeps me from doing what I want to do 4
I have fatigue that prevents me from working 5
I have fatigue that prevents me from working and requires that I have assistance to carry out normal activities of living 6
I am worse off than any of these statements suggest 7

12. How frequently are you bothered by fatigue *(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
Less frequently 5

13. Is your fatigue typically present *(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

14. Is your fatigue typically worse the day after a period of extra activity or exercise:

Yes ..... (1)
No 2

Affix label here

Patient ID: 9055
Patient code: AHA
Visit code: S1

15. Do you believe that your fatigue is due to your liver problem (as opposed to something else, like not getting enough sleep, depression or being out of shape):

Circle one

Yes ..... (1)
No 2

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

Very good 1
Good ..... (2)
Fair 3
Poor 4
Awful 5

17. Today's date:

6/14/04

Thank you for completing this questionnaire.

AD – Alcohol Use Disorders Identification Test (AUDIT)

Keyed: ( )
DRAFT

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 spouse or family. Clinical Coordinator/parent can assist patients age 8-12.
Instructions: Flash Card #15, 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: 9 0 5 5
3. Patient code: A H A
4. Date of visit *(date patient completed the form)*:
   0 4 - J U N - 0 4
   day mon year
5. Visit code: s 1 ____ ____
6. Form & revision: a d 0
7. Study *(check only one)*: NAFLD Database 1

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: 9 0 3
    - b. Signature: Cindy Coordinator
11. Date form reviewed:
    0 7 - J U N - 0 4
    day mon year

Patient ID: 9055

DRAFT

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)

DRAFT

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:

6/4/04

Thank you for completing this questionnaire.

NAFLD Database

PE - Physical Examination

DRAFT

Purpose: Record detailed physical exam findings.
When: Visits s1, f048, f096, f144, and f192.
Administered by: Study Physician and Clinical Coordinator.
Respondent: Patient.
Instructions: Use a calculator for all calculations.

A. Center, patient, and visit identification

1. Center ID: ____ ____ - ____ ____
2. Patient ID: 9055
3. Patient code: AHA
4. Visit date: 27 - MAY - 04 (day - mon - year)
5. Visit code: 31
6. Form & revision: p e 0
7. Study: NAFLD Database 1

B. Measurements

8. Units of height measurement performed:
   - Inches (✓1)
   - Centimeters (2)

   9b.

9. Height *(shoes off)*
   - a. Height in inches: 68 • 5 (in)
   - b. Height in centimeters *(measured directly or item 9a x 2.54)*: 174 • 0 (cm)

10. Units of weight measurement performed:
    - Pounds (✓1)
    - Kilograms (2)

    11b.

11. Weight *(shoes off)*
    - a. Weight in pounds: 273 • 5 (lb)
    - b. Weight in kilograms *(measured directly or item 10a/2.2046)*: 124 • 1 (kg)

12. Body mass index, BMI *(kg/m^2; weight/[(ht/100)^2]; item 11b/(item 9b)^2; use a calculator)*: 41 • 0 (kg/m^2)

13. Waist *(standing, at umbilicus)*
    - a. Circumference: 052 • 4 (waist circumference)
    - b. Scale:
      - Inches (✓1)
      - Centimeters (2)

14. Hip *(standing, at widest part of the hips)*
    - a. Circumference: 054 • 5 (hip circumference)
    - b. Scale:
      - Inches (✓1)
      - Centimeters (2)

15. Waist to hip ratio *(waist circumference/hip circumference; use a calculator)*: 0 • 961 (waist circumference/hip circumference)

16. Temperature *(Oral or other, as appropriate for age)*
    - a. Degrees: 098 • 7
    - b. Scale:
      - Fahrenheit (✓1)
      - Centigrade (2)

Patient ID: 9055

17. Blood pressure

a. Systolic: 145 mmHg

b. Diastolic: 087 mmHg

18. Resting radial pulse: 092 beats/minute

19. Respiratory rate: 24 breaths/minute

C. Examination findings

20. Skin:

Normal (✓1)

21.

Abnormal (2)

specify abnormality

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

Normal (✓1)

22.

Abnormal (2)

specify abnormality

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 abnormality

25. Heart:

Normal (✓1)

26.

Abnormal (2)

specify abnormality

26. Abdomen:

Normal (✓1)

27.

Abnormal (2)

specify abnormality

27. Liver and spleen:

Normal (1)

29.

Abnormal (✓2)

28. Abnormality *(check all that apply)*

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

b. Splenomegaly: (✓1)

c. Ascites: (1)

d. Pedal edema: (1)

e. Jaundice: (1)

f. Asterixis: (✓1)

g. Contractures: (1)

h. Spider angiomata: (1)

i. Hepatic encephalopathy: (1)

j. Palmar erythema: (1)

k. Acanthosis nigricans: (1)

l. Muscle wasting: (1)

29. Extremities:

Not performed (9)

Normal (✓1)

30.

Abnormal (2)

specify abnormality

30. Genitourinary/pelvis:

Not performed (✓0)
Normal (1)
Abnormal (2)

31.

_____
specify abnormality

31. Nervous system:

Not performed (✓0)
Normal (1)
Abnormal (2)

32.

_____
specify abnormality

D. Tanner Staging

32. Is Tanner staging required for this participant *(check only one):*

Yes, participant has not reached full sexual maturity and is 17 years old or younger: (1)
No, participant is 18 years old or older (✓2)
No, participant had reached full sexual maturity *(Tanner stage 5 on all parameters at screening or for 2 consecutive visits)* (3)

40.

Male Tanner Staging

33. Genital stage: ____ 1-5

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

35. Pubic hair stage: ____ 1-5

Female Tanner Staging

36. Breast stage: ____ 1-5

37. Pubic hair stage: ____ 1-5

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

40.

39. What was the participant's age at menarche: ____ ____ age in years

E. Administrative information

40. Study Physician PIN: 910

41. Study Physician signature: Noelle Nash

42. Clinical Coordinator PIN: 903

43. Clinical Coordinator signature: Cindy Coordinator

44. Date form reviewed: 28 - MAY - 04
day mon year

NAFLD Database

LS - Laboratory Results - Tests Done only During Screening

DRAFT

Purpose: To record archival and current results of laboratory tests done only at screening.
When: Visit s1.
Administered by: Study Physician (adult hepatologist or pediatrician) 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.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____
2. Patient ID: 9055
3. Patient code: AHA
4. Date of visit: 27 - MAY - 04 (day - mon - year)
5. Visit code: s1 ____ ____
6. Form & revision: 1s0
7. Study: NAFLD Database 1

B. Screening etiologic tests

8. Date of blood draw for serological assays to exclude viral causes of chronic liver disease: 04 - JUN - 01 (day - mon - year)

Repeat if date is greater than 5 years prior to screening.
If the patient is judged by Study Physician to have a high-risk lifestyle, repeat if date is greater than 6 months prior to screening.

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

b. Hepatitis B core antibody (anti-HBc):
- Positive ( ) 1
- Negative (✓) 2

c. Hepatitis B surface antibody (anti-HBs):
- Positive ( ) 1
- Negative (✓) 2

d. Hepatitis C antibody (anti-HCV):
- Positive ( ) Elig
- Negative (✓) 2

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

f. Hepatitis A virus antibody (anti-HAV, total):
- Positive ( ) 1
- Negative ( ) 2
- Not available (✓) 3

Patient ID: 9055

C. Iron

9. Date of blood draw for iron overload screening:

31 - JUL - 02
day mon year

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

a. Iron: 110 µg/dL

b. Total iron binding capacity: 250 µg/dL

c. Ferritin: 0065 ng/mL

10. Is hepatic iron index available:

( ) Yes (1) (✓) No (2)

12.

11. Hepatic iron index: ___ • ___

D. HFE gene analysis

12. Does the patient have an abnormality in an iron overload screening test, a family history of iron overload or hemochromatosis, or histological iron of greater than 3+:

(✓) Yes (1) ( ) No (2)

15.

13. Date of blood draw for HFE gene analysis:

31 - OCT - 01
day mon year

14. Type of abnormality *(WT = wild type; check only one):*

None	(✓ 0)
C282Y/H63D heterozygote mutation	(1)
C282Y/C282Y homozygote mutation	(2)
C282Y/WT heterozygote mutation	(3)
H63D/WT heterozygote mutation	(4)
H63D/H63D homozygote mutation	(5)

E. Ceruloplasmin

15. Is patient 40 years old or younger:

( ) Yes (1) (✓) No (2)

18.

16. Date of blood draw for ceruloplasmin: *(required only if patient is 40 years old or younger):*

___ - ___ - ___
day mon year

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

17. Ceruloplasmin ___ • ___ mg/dL

a. Upper limit of normal: ___ • ___ mg/dL

b. Lower limit of normal: ___ • ___ mg/dL

F. Alpha-1 antitrypsin

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

03 - AUG - 99
day mon year

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

19. Alpha-1 antitrypsin (A1AT)

165 • 7

a. Upper limit of normal:

200 • 0

b. Lower limit of normal:

050 • 0

20. A1AT phenotype

a. Pi Z heterozygote:

( ) Yes (1) (✓) No (2)

b. Pi ZZ homozygote:

( ) Yes (1) (✓) No (2)

21. A1AT deficiency *(physician judgment):*

( ) Yes (1) (✓) No (2)

Patient ID: 9055

G. Autoantibody studies

22. Date of blood draw for autoantibody tests:

03 - JUL - 00
day mon year

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

23. Antinuclear antibody (ANA):

Positive (1)
Negative (✓2)

24.

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

24. Antismooth muscle antibody (ASMA):

Positive (1)
Negative (✓2)

25.

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

25. Antimitochondrial antibody (AMA):

Positive (1)
Negative (✓2)

26.

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

26. Is the patient 18 or older:

Yes (✓1) No (2)

30.

27. Lymphocytotoxic antibody (LCA):

Positive (1)
Negative (2)

28.

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

28. Antibody to liver-kidney microsomal antigen (LKM1):

Positive (1)
Negative (2)

35.

a. If positive, LKM1: 1/____ ____ ____ ____

29. Rheumatoid factor (RF):

Positive (1)
Negative (2)

30.

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

H. Immunoglobulin levels

30. Are immunoglobulin levels available:

Yes (✓1) No (2)

35.

31. Date of blood draw for immunoglobulin levels:

09 - JUN - 02
day mon year

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

32. IgA: 04.3 mg/dL

33. IgG: 15.1 mg/dL

34. IgM: 00.9 mg/dL

I. Other screening blood tests

35. Date of blood draw for thyroid stimulating hormone (TSH):

16 - SEP - 03
day mon year

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

36. Thyroid stimulating hormone: 02.53 µU/mL

Patient ID: 9055

J. Administrative information

37. Study Physician PIN: 910

38. Study Physician signature: Neville Nash

39. Clinical Coordinator PIN: 903

40. Clinical Coordinator signature: Cindy Coordinator

41. Date form reviewed: 01 JUN 04
day mon year

Purpose: To obtain the patient's physical activity.
When: Visits s2, f048, f096, f144, and f192.
Administered by: Self-administered, but Clinical Coordinator must be available at visits to answer questions and review completed forms.
Respondent: Patient, 18 years of age or older, without help from spouse or family.
Instructions: The Clinical Coordinator should complete section A below and attach a label to each of pages 2-4. **Screening:** The patient should meet with the Clinical Coordinator, be trained in 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 complete section B below. **Followup:** Pages 2-4 should be mailed to the patient 2 weeks prior to the scheduled study visit with instructions to complete the form at home and to bring the completed form to the next study visit. When the patient returns for the visit, the Clinical Coordinator should review the form for completeness and obtain responses for missing items during the visit. If the patient did not bring a completed form to the visit, the patient should complete the form at the visit. Page 1 should be reattached to pages 2-4 and the Clinical Coordinator should complete section B. Item 4 should be completed with the date the patient wrote in item 39. If the patient did not write in a date, use the date of the study visit for the visit date.

A. Center, patient, and visit identification

1. Center ID: ____
2. Patient ID: 9055
3. Patient code: AHA
4. Date of visit *(date patient completed the form)*: 03 (day) - JUN (mon) - 04 (year)
5. Visit code: S2
6. Form & revision: **pa0**
7. Study: NAFLD Database 1

B. Administrative information

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

8. Clinical Coordinator
   a. PIN: 903
   b. Signature: Cindy Coordinator
9. Date form reviewed: 07 (day) - JUN (mon) - 04 (year)

Affix label here

Patient ID: 9055

Patient code: AHA

Visit code: S2

PA - Physical Activity

Instructions: This survey asks for your views about your physical activity. *(Items 1-9 are reserved for clinical center use).*

C. Non-Recreational Activity (Work Related)

The following questions are about your non-recreational activity. Non-recreational activity is what you consider your main day to day activity, at work or at home, whether you get paid or not.

Circle one

10. Level of activity that best describes your usual non-recreational activity.

Vigorous or strenuous activity: 1
(involves heavy lifting, digging, handling heavy tools or equipment, or any other activity causing you to work up a sweat or get out of breath)

Moderate activity: 2
(requires moderate-paced walking on a flat surface, heavy one-arm work or moderate two-arm work, such as picking, sweeping, lifting light objects, or heavy housework)

Light activity: ..... (3)
(involves sitting down with one hand movement, moderate one-arm work or light two-arm work, with occasional walking or standing such as office work, filing or sorting, or light or moderate housework)

11. On average, how many hours per day do you spend at this level of activity?

10 Hours

12. On average, how many hours per day do you spend sitting down?

09 Hours

D. Recreational Activity (Non-Work Related)

The following questions are about the recreational activities you spend at least 15 minutes doing each week. You should count walking or biking to work and any other activities outside of work. Next to each activity that you participate in, write in how many total hours or minutes you do that activity on an average week. Mark the places for hours and minutes only for the activities you participate in.

For each activity that you engage in for at least 15 minutes per week, please circle the activity and write the number of hours or minutes that you do that activity per week.	
13. Swimming	Hours: ____ ____ Minutes: ____ ____
14. Jogging	Hours: ____ ____ Minutes: ____ ____
15. Running	Hours: ____ ____ Minutes: ____ ____
16. Brisk walking	Hours: 0 3 Minutes: 0 0
17. Bicycling on hills	Hours: ____ ____ Minutes: ____ ____
18. Bicycling on flat surfaces	Hours: ____ ____ Minutes: ____ ____
19. Hiking or climbing	Hours: ____ ____ Minutes: ____ ____
20. Yard work / Gardening	Hours: 0 8 Minutes: 4 5
21. Aerobics	Hours: ____ ____ Minutes: ____ ____
22. Dancing	Hours: ____ ____ Minutes: ____ ____
23. Calisthenics (exercises without machines)	Hours: ____ ____ Minutes: ____ ____
24. Weight lifting, using weight machines, or heavy lifting	Hours: 0 2 Minutes: 3 0
25. Treadmill or Stairmaster	Hours: ____ ____ Minutes: ____ ____
26. Chopping wood	Hours: ____ ____ Minutes: ____ ____

Affix label here

Patient ID: 9055
Patient code: AHA
Visit code: S2

For each activity that you engage in for at least 15 minutes per week, please circle the activity and write the number of hours or minutes that you do that activity per week.	
27. Painting / Woodworking	Hours: ____ ____ Minutes: ____ ____
28. Housecleaning	Hours: ____ ____ Minutes: ____ ____
29. Golfing	Hours: 0 5 Minutes: 0 0
30. Singles tennis, racquetball, or other court sports	Hours: ____ ____ Minutes: ____ ____
31. Doubles tennis, racquetball or other court sports	Hours: ____ ____ Minutes: ____ ____
32. Basketball	Hours: ____ ____ Minutes: ____ ____
33. Football, soccer, or other field sports	Hours: ____ ____ Minutes: ____ ____
34. Skiing	Hours: ____ ____ Minutes: ____ ____
35. Bowling	Hours: ____ ____ Minutes: ____ ____
Others *(write in the name of activity)*:	
36. Name of activity _____	Hours: ____ ____ Minutes: ____ ____
37. Name of activity _____	Hours: ____ ____ Minutes: ____ ____
38. Name of activity _____	Hours: ____ ____ Minutes: ____ ____

39. Today's date:

6/3/04

Thank you for completing this survey. Please bring this completed survey with you to your scheduled NASH CRN study visit.

NAFLD Database

IR - Liver Imaging Studies Report

DRAFT

Purpose: To record liver imaging study results.
When: Visits s2, f024, f048, f096, f144, and f192.
Administered by: Clinical Coordinator.
Instructions: Complete this form at each of the visits listed above; the form will allow you to skip out of sections that are irrelevant to your patient. What you will report at each visit are the results of the most recent scan of each type done in the year prior to screening (visit s2) or in the period since the prior study visit (after enrollment). These will likely be standard of care scans with results obtained via medical records. In each case, answer the items based on review of the report; the Study Physician must review and approve the findings recorded on this form. Liver imaging studies available at baseline and during followup should be reported on this form even if the patient has definite NAFLD or cryptogenic cirrhosis by histology.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____
2. Patient ID: 9 0 5 5
3. Patient code: A H A
4. Date of visit: 07 - JUN - 04 (day - mon - year)
5. Visit code: S 2 ____ ____
6. Form & revision: i r 0
7. Study: NAFLD Database 1

B. Upper abdominal ultrasound

8. Did the patient have an upper abdominal ultrasound in the past year *(screening)*/ since the last visit *(followup)*: (Yes ✓ 1) (No 2) → 11.
9. Date of most recent upper abdominal ultrasound: 12 - DEC - 03 (day - mon - year)

10. 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. Intrahepatic biliary dilatation:	(1)
f. Extrahepatic biliary dilatation:	(1)
g. Gallstones/cholelithiasis:	(✓ 1)
h. Gall bladder polyps:	(1)
i. Cholecystectomy:	(1)
j. Splenomegaly:	(1)
k. Ascites:	(1)
l. Other features of portal hypertension *(specify)*:	(1)
m. Other abnormality *(specify)*:	(1)
n. None of the above:	(1)

Patient ID: 9055

C. Upper abdominal CT scan

11. Did the patient have an upper abdominal CT scan in the past year *(screening)*/ since the last visit *(followup)*:

( ) Yes (1) (✓) No (2)

→ **14.**

12. Date of most recent upper abdominal CT scan:

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

13. 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. Gallstones/cholelithiasis: (1)
j. Gall bladder polyps: (1)
k. Cholecystectomy: (1)
l. Splenomegaly: (1)
m. Ascites: (1)
n. Other features of portal hypertension *(specify):* (1)

_____

_____

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

_____

_____

p. None of the above: (1)

D. Upper abdominal MRI

14. Did the patient have an upper abdominal MRI in the past year *(screening)*/since the last visit *(followup*:

( ) Yes (1) (✓) No (2)

→ **17.**

15. Date of most recent upper abdominal MRI:

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

16. 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)

E. Administrative information

17. Study Physician PIN: 910

18. Study Physician signature: Neville Nash

19. Clinical Coordinator PIN: 903

20. Clinical Coordinator signature: Cindy Coordinator

21. Date form reviewed: 10-JUN-04
day mon year

Purpose: To obtain the patient's views of his/her health.
When: Visits s2, f048, f096, f144, and f192.
Administered by: Self-administered, but Clinical Coordinator must be available at visits to answer questions and to review completed forms.
Respondent: Patient, 18 years or age or older, without help from spouse or family.
Instructions: The Clinical Coordinator should complete section A below and attach a label to each of pages 2-7.
Screening: The patient should meet with the Clinical Coordinator, be trained in completion of the form, and then should complete pages 2-7. 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 2-7 and the Clinical Coordinator should complete section B below. **Followup:** Pages 2-7 should be mailed to the patient 2 weeks prior to the scheduled study visit with instructions to complete the form at home and to bring the completed form to the next study visit. When the patient returns for the visit, the Clinical Coordinator should review the form for completeness and obtain responses for missing items during the visit. If the patient did not bring a completed form to the visit, the patient should complete the form at the visit. Page 1 should be attached to pages 2-7 and the Clinical Coordinator should complete section B below. Fill in item 4 with the date the patient wrote in item 21. If the patient did not write in a date, use the date of the study visit for the visit date.

A. Center, patient, and visit identification

1. Center ID: ____ ____ ____ ____
2. Patient ID: 9 0 5 5
3. Patient code: A H A
4. Date of visit *(date patient completed the form)*: 0 3 - J u N - 0 4 (day - mon - year)
5. Visit code: S 2 ____ ____
6. Form & revision: q f 0
7. Study: NAFLD DATABASE 1

B. Administrative information

(To be completed by clinical center staff after survey is completed.)

8. Clinical Coordinator
   a. PIN: 9 0 3
   b. Signature: Cindy Coordinator
9. Date form reviewed: 0 7 - J u N - 0 4 (day - mon - year)

Affix label here

Patient ID: 9055
Patient code: AHA
Visit code: S2

QF - MOS 36-Item Short-Form Health Survey

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

(Items 1-9 are reserved for clinical center use.)

10. In general, would you say your health is:

	Circle one
Excellent	1
Very good	(2)
Good	3
Fair	4
Poor	5

11. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	(3)
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

12. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Activities	**Circle one**		
	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports:	1	(2)	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:	1	2	(3)
c. Lifting or carrying groceries:	1	2	(3)
d. Climbing several flights of stairs:	1	2	(3)
e. Climbing one flight of stairs:	1	2	(3)
f. Bending, kneeling, or stooping:	1	(2)	3
g. Walking more than a mile:	1	(2)	3
h. Walking several blocks:	1	2	(3)
i. Walking one block:	1	2	(3)
j. Bathing or dressing yourself:	1	2	(3)

Affix label here	
Patient ID:	9055
Patient code:	AHA
Visit code:	S2

13. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Circle one	
	Yes	**No**
a. Cut down on the amount of time you spent on work or other activities:	1	(2)
b. Accomplished less than you would like:	(1)	2
c. Were limited in the kind of work or other activities:	(1)	2
d. Had difficulty performing the work or activities (for example, it took extra effort):	1	(2)

14. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Circle one	
	Yes	**No**
a. Cut down on the amount of time you spent on work or other activities:	1	(2)
b. Accomplished less than you would like:	(1)	2
c. Didn't do work or other activities as carefully as usual:	1	(2)

15. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Circle one

Not at all 1
Slightly . . . . . (2)
Moderately 3
Quite a bit 4
Extremely 5

16. How much bodily pain have you had during the past 4 weeks?

None 1
Very mild . . . . . (2)
Mild 3
Moderate 4
Severe 5
Very severe 6

Affix label here	
Patient ID:	9055
Patient code:	AHA
Visit code:	S2

17. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all ..... (1)
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

18. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

	Circle one					
	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a. Did you feel full of pep?	1	2	3	(4)	5	6
b. Have you been a very nervous person?	1	2	3	4	5	(6)
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	(6)
d. Have you felt calm and peaceful?	1	2	(3)	4	5	6
e. Did you have a lot of energy?	1	2	3	(4)	5	6
f. Have you felt downhearted and blue?	1	2	3	4	(5)	6
g. Did you feel worn out?	1	2	(3)	4	5	6
h. Have you been a happy person?	1	2	3	(4)	5	6
i. Did you feel tired?	1	2	(3)	4	5	6

Affix label here	
Patient ID:	9055
Patient code:	AHA
Visit code:	S2

19. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

	Circle one
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	(4)
None of the time	5

20. How TRUE or FALSE is *each* of the following statements for you.

	Circle one				
	Definitely true	**Mostly true**	**Don't know**	**Mostly false**	**Definitely false**
a. I seem to get sick a little easier than other people	1	2	3	(4)	5
b. I am as healthy as anybody I know	1	(2)	3	4	5
c. I expect my health to get worse	1	2	(3)	4	5
d. My health is excellent	1	(2)	3	4	5

21. Today's date:

6/3/04

Thank you for completing this survey. Please bring this completed survey with you to your scheduled NASH CRN study visit.

NAFLD Database

ED - Database Enrollment

DRAFT

Purpose: • Check eligibility for NAFLD Database.
• Check completion of required assessments and conformance with required time windows.
• Alert you to findings which will render the patient ineligible if unchanged at the time of randomization.
• Record reasons for ineligibility for patients found to be ineligible prior to starting rehabilitation.

When: Visit s2.

Administered by: Study Physician (adult hepatologist or pediatrician) and Clinical Coordinator.

Respondent: Patient and Clinical Coordinator.

Instructions: If Elig is checked for any item, complete the entire form but note that the patient may not continue in the NAFLD Database. If an item has not been assessed because the patient is ineligible, write "m" (missing) next to that item. This form should be keyed for each patient for whom Form RG was completed without encountering a STOP or Elig condition.

A. Center, patient, and visit identification

1. Center ID: ____ __ ____ ____
2. Patient ID: 9055
3. Patient code: AHA
4. Visit date *(date this form is initiated)*: 11 - JUN - 04 (day - mon - year)
5. Visit code: s2 ____ ____
6. Form & revision: ed 0
7. Study: NAFLD Database 1

B. Alcohol use history consistent with NAFLD

8. On average, how many drinks containing alcohol has the patient had per week in the 2 years prior to screening:

Less than one drink a week	(1)
One drink a week	(✓2)
2 to 4 drinks a week	(3)
5 to 7 drinks a week	(4)
8 to 10 drinks a week	(*5)
11 to 14 drinks a week	(*6)
15 or more drinks a week	(7) Elig

** Patient is ineligible if female*

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

Yes (✓1) No (2) Elig

C. Exclusions

10. Do any of the patient's assessments show evidence of these medical exclusions

a. Total parenteral nutrition (TPN) within 3 months prior to screening:

Yes (1) Elig No (✓2)

b. Short bowel syndrome:

Yes (1) Elig No (✓2)

c. History of gastric or jejunoileal bypass prior to the diagnosis of NAFLD *(bariatric surgery performed concomitant with or following the diagnosis of NAFLD is not exclusionary)*:

Yes (1) Elig No (✓2)

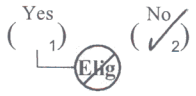
d. History of biliopancreatic diversion:

Yes (1) Elig No (✓2)

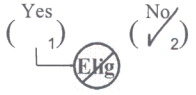
e. Evidence of advanced liver disease *(Child-Pugh-Turcotte score at least 10)*:

Yes (1) Elig No (✓2)

f. Evidence of chronic hepatitis B as marked by the presence of HBsAg in serum *(patients with isolated anti-HBc are not excluded):*



g. Evidence of chronic hepatitis C as marked by the presence of anti-HCV or HCV RNA in serum:

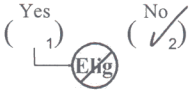


h. Low alpha-1-antitrypsin level and ZZ phenotype *(physician judgment):*

i. Wilson's disease:

j. Known glycogen storage disease:

k. Known dysbetalipoproteinemia:

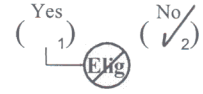


l. Known phenotypic hemochromatosis (removal of > 4 g of iron by phlebotomy in an individual 18 or older):

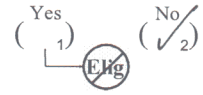
m. Congenital hepatic fibrosis, polycystic liver disease:

n. Other metabolic/congenital liver disease:

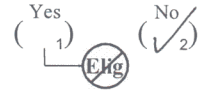
o. HIV infection or other systemic infectious disease:



p. Disseminated or advanced extrahepatic malignancy:

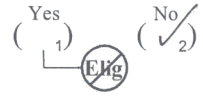


q. Other severe systemic illness that in the opinion of the investigator would interfere with completion of followup:

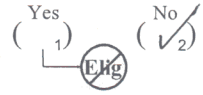


11. Do any of the patient's assessments show evidence of these histologic exclusions

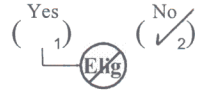
a. Hepatic iron index > 1.9:



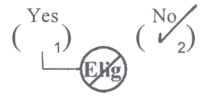
b. Iron overload greater than 3+:



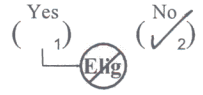
c. Prominent bile duct injury *(florid duct lesions or periductal sclerosis)* or bile duct paucity:



d. Chronic cholestasis:



e. Vascular lesions *(vasculitis, cardiac sclerosis, acute or chronic Budd-Chiari, hepatoportal sclerosis, peliosis):*



f. Zones of confluent necrosis, infarction, massive or sub-massive, pan-acinar necrosis:

( ) Yes (1) — Elig

(✓) No (2)

g. Multiple epithelioid granulomas:

( ) Yes (1) — Elig

(✓) No (2)

12. Is there any other condition or issue that, in the opinion of the investigator, would interfere with the patient's adherence to study requirements:

( ) Yes (1) — Elig

(✓) No (2)

D. Check on imaging and histologic criteria for inclusion in Database

13. Does the patient have at least 5% steatosis on biopsy:

- Yes (✓ 1)
- No (2)
- No biopsy available (3)

14. Does the patient have cryptogenic cirrhosis on biopsy *(cirrhosis but with less than 5% steatosis):*

- Yes (1)
- No (✓ 2)
- No biopsy available (3)

15. Does the patient have an imaging study suggestive of NAFLD *(physician judgment, criteria not specified):*

(✓) Yes (1)

( ) No (2) — 17.

16. Imaging studies suggestive of NAFLD *(check all that apply)*

- **a.** Upper abdominal ultrasound: (✓ 1)
- **b.** Upper abdominal CT scan: (1)
- **c.** Upper abdominal MRI: (1)

17. Does the patient have an imaging study compatible with cirrhosis *(small liver, nodularity, heterogeneous echo pattern):*

( ) Yes (1)

(✓) No (2) — 20.

18. Imaging studies suggestive of cirrhosis *(check all that apply)*

- **a.** Upper abdominal ultrasound: (1)
- **b.** Upper abdominal CT scan: (1)
- **c.** Upper abdominal MRI: (1)

19. Does the patient have any of the following findings

- **a.** Imaging evidence of portal hypertension *(splenomegaly, portosystemic collaterals):* (1)
- **b.** Albumin less than 3.5 g/dL: (1)
- **c.** INR greater than 1.3: (1)
- **d.** Platelet count less than 140,000 cells/uL: (1)
- **e.** Esophageal or gastric varices on endoscopy: (1)
- **f.** Ascites on physical exam or imaging study: (1)
- **g.** None of the above: (1)

E. Diagnostic category for inclusion

20. Diagnostic category for inclusion *(check only one):*

- Definite NAFLD *(item 13 = Yes)* (✓ 1)
- Definite cryptogenic cirrhosis *(item 14 = Yes)* (2)
- Suspected NAFLD *(item 15 = Yes)* (3)
- Suspected (clinical) cryptogenic cirrhosis *(item 17 = Yes and at least one of items 19a-f is checked)* (4)
- None of the above (5) — Elig

Patient ID: 9055

F. Date, numeric, and form specific checks and summary check on eligibility

Instructions: Key visits s1 and s2 forms: RG and AD, BC, BD, BG, BP, CG, HF, IR, LD, LP/LQ, LR, LS, PA/MA, PE, PF, QF/PQ, PR, PS, PT, PV, PW, PY as appropriate. Run the Eligibility Check task on your clinic data system.

21. Were any STOP's or ineligible conditions other than "missing Form ED" identified by the Eligibility Check task:

Yes (1)
No (✓2)
Task not run (3)

22. Eligibility status *(check all that apply)*

a. "No" checked for item 21: (✓1)
24. ___

b. "Yes" checked for item 21: (1)
23. ___

c. Ineligibility condition checked in items 8-12 or item 20: (1)
23. ___

G. Reasons for ineligibility for ineligible patients

NOTE: Complete this section for ineligible patients only.

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

a. Reason covered in items 8-12 or item 20: (1)

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

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

_____

H. Administrative information

24. Study Physician PIN: 910

25. Study Physician signature: Neville Nash

26. Clinical Coordinator PIN: 903

27. Clinical Coordinator signature: Cindy Coordinator

28. Date form reviewed: 14 (day) JUN (mon) 04 (year)

NASH CRN

Nonalcoholic Steatohepatitis
Clinical Research Network

CyNCh
Standard Operating Procedures
Part IV:

Liver Biopsy
and
Histology Scoring System

April 2012

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CyNCh SOP IV: Biopsy and Histology Scoring

1. Overview

1.1. Philosophy

Nonalcoholic fatty liver disease (NAFLD) is defined by hepatic steatosis in the absence of known causes of liver disease and significant alcohol consumption. Nonalcoholic steatohepatitis (NASH) is a subset of NAFLD defined histologically by steatosis, spotty lobular inflammation, and distinctive pattern of zone 3 injury characterized by hepatocellular ballooning; Mallory's hyaline and perisinusoidal fibrosis (psf) may also be present. In some as yet poorly defined fraction of patients, there is progression of disease to cirrhosis and hepatocellular carcinoma. The NASH Clinical Research Network (NASH CRN) is a clinical research network sponsored by the NIDDK to study the natural history of NAFLD in both adult and pediatric patients and to carry out (1) treatment trials of NASH in adult patients and (2) treatment trials of NAFLD in pediatric patients. This document specifies the procedures for liver biopsy and histology scoring for the CyNCh trial which will evaluate whether 52 weeks of treatment with delayed release (DR) cysteamine in children improves NAFLD as measured by changes in histology, compared to treatment with placebo. Procedures for other NASH CRN studies, including the NAFLD Database 2 and FLINT trial, will be specified in separate manuals specific to the particular study.

The procedures specified by the NASH CRN for their studies are based on two concepts: one is the principle that a primary goal of the NASH CRN is to collect a database of specimens along with clinical and laboratory data, so that this information remains available for research after the NASH CRN has disbanded. The other concept behind these procedures is the necessity of a system of evaluation of NASH that can be utilized in evaluating efficacy in treatment trials. Because there are no serum markers or other diagnostic modalities that can accurately stage or grade the liver disease in these patients, a liver biopsy remains the standard against which all other methods will be compared. Every effort should be made to build a liver tissue archive and slide archive that are as complete as possible, so that what is accomplished will have value for the future as well as the present. With this principle in mind, study consent statements should include language that permits such approved uses of liver biopsy materials without the need for re-consent at a later date; patients who refuse access to their liver biopsies or who refuse to provide specimens for banking should not be enrolled in the NASH CRN.

1.1. Philosophy

Histologically confirmed NAFLD is an inclusion criterion for the CyNCh trial. The baseline biopsy may have been done prior to screening (within specified time limits) or it may be done as standard of care as part of the screening procedure. CyNCh patients will also have a followup biopsy after 52 weeks of treatment in the trial. Unscheduled biopsies also may occur after screening. Ideally, the CyNCh trial will obtain a piece of liver tissue for banking and 10 unstained slides for archiving from each of these biopsies. However, because some of the biopsies evaluated for CyNCh may not provide these materials (eg, not enough tissue is obtained or the paraffin block is exhausted), contingency plans have been developed, including requesting to borrow the institutional slides and returning them after central scoring has been completed.

It should be emphasized that a surgical pathology report alone is not sufficient for satisfying inclusion/exclusion criteria related to liver histology nor for comparison with other biopsy data. Tissue slides must be available for review and must be judged by the CyNCh pathologist to be adequate for scoring according to the NASH CRN scoring protocol. However, a copy of the surgical pathology report must be obtained for all slides. The surgical pathology report serves two purposes: (1) to verify and document the identity of the patient whose tissue is on the slides that are being evaluated and (2) to provide the date of the biopsy.

1.2. Tasks and forms related to liver biopsy

The CyNCh eligibility criteria include histologic evidence of NAFLD according to the NASH CRN protocol for histology scoring. The biopsy that is used to satisfy eligibility may be a historical biopsy (done in the 120 days prior to enrollment and the patient must not have used specified medications in the 90 days prior to the biopsy) or it may be done prospectively under the care of the CyNCh investigator as a screening procedure. Each randomized patient will have another biopsy after 52 weeks of treatment. In addition, a patient may have an interim biopsy as needed for standard of care. As a check to be sure that all biopsies that occur are caught, occurrence of a biopsy since the previous CyNCh visit is queried on the Followup Medical History (HI) form.

Information about the biopsy procedure and materials is captured on the Liver Biopsy Materials Documentation (SD) form. Cautions about the use of proscribed medications in the 90 days prior to the biopsy used for eligibility screening are noted on the Baseline History (BH) form; lack of use of proscribed medications is confirmed on the Liver Biopsy Materials Documentation (SD) form. The SD form also documents the outcome of the biopsy with regard to availability of tissue for banking and availability of stained and unstained slides for scoring and archiving. If tissue was obtained for banking, the Liver Tissue Banking (LT) form must be completed. If the biopsy was a screening biopsy (ie, done/evaluated to determine eligibility for CyNCh), then the local CyNCh Study Pathologist must complete the Liver Biopsy Histology Worksheet (HW) form. If the NAFLD activity score (NAS) for the screening biopsy is less than 4, then the patient is not eligible for CyNCh but may be an appropriate candidate for the Pediatric Database 2 Study. Other forms that the CyNCh trial uses to document activities and materials related to liver biopsy are the Liver Biopsy Histology

1.2. Tasks and forms related to liver biopsy

Findings (HF) form and Central Histology Review (CR) form and logs for shipping tissue and slides (forms SS and TS). In summary, these seven forms (SD, LT, HW, HF, CR, TS, SS) are used to:

- Document what slides, if any, are available for scoring and sending to the DCC and whether liver tissue was obtained for banking (form SD)
- If the biopsy is the screening biopsy, document lack of use of proscribed medications during the 90 days prior to the biopsy (form SD) and remind the clinical center that the screening biopsy cannot be older than 120 days at the time of randomization
- If liver tissue was obtained for banking, document collection of extra liver tissue and procedures for banking (form LT)
- Document local scoring of baseline biopsies (forms HW and HF)
- Document shipment of slides to the DCC (form TS)
- Document shipment of liver tissue in RNA*later*® Solution to the Biosample Repository (Form SS)
- Document scoring of baseline and followup biopsies by the NASH CRN Pathology Committee (form CR)

The CyNCh hepatologist, the Study Pathologist, and the Clinical Coordinator must work together to accomplish these tasks and complete the required forms. Considerable cooperation and close communication will be required to complete these tasks successfully.

2. Obtaining liver biopsy materials for scoring for CyNCh

2.1. Overview

Baseline (screening) liver biopsy specimens can be divided into two categories: (1) those performed prior to consent for screening, and (2) those performed as part of standard of care during the screening process, but after consent for screening for CyNCh has been obtained. In the case of (1), we will try to obtain 10 unstained slides for the exclusive use by CyNCh, but limited biopsy materials may require that the institution's biopsy slides be borrowed. In the case of (2), sufficient tissue should be collected to provide for the institutional pathology slides AND 10 unstained slides for CyNCh exclusive use AND for banking a sample at the Biosample Repository. Followup liver biopsies should all be in category (2).

Baseline biopsies will be scored by the local CyNCh Study Pathologist (to determine eligibility) and also centrally (after randomization) by the Pathology Committee. Biopsies obtained 52 weeks after randomization will be scored centrally only by the Pathology Committee. Unscheduled biopsies will be read locally for standard of care and will also be scored centrally by the Pathology Committee.

2.2. Baseline biopsies performed prior to consent for screening

Because these biopsies were obtained prior to consent for CyNCh screening, investigators may have little control over variables such as fixation or biopsy size, but these considerations should not prevent investigators from trying to obtain unstained slides for CyNCh purposes. However, it is an unfortunate fact that the amount of tissue available in archived paraffin blocks may be very limited.

Upon learning that a patient had a recent biopsy and after checking that no proscribed medications were used in the 90 days prior to the biopsy, the Clinical Coordinator should obtain the original pathology materials: the surgical pathology report, the institution's H&E and Masson's trichrome slides, and the paraffin block so that 10 unstained slides may be obtained (see below for how to prepare and label those slides).

Upon receipt of the original pathology materials, the Clinical Coordinator should verify that all materials pertain to the CyNCh patient they are said to and should annotate the surgical pathology report with the patient's NASH CRN ID number and code and black out the patient's name. The annotated report should be attached to the Liver Biopsy Materials Documentation (SD) form and a copy of the annotated report must be sent to the DCC when the biopsy slides are sent to the DCC. The Clinical Coordinator and/or Study Pathologist must determine the following so that form SD may be completed:

2.2. Baseline biopsies performed prior to consent for screening

- Confirm that no proscribed medications were used in the 90 days prior to the biopsy (baseline biopsy only)
- Determine the number and type of the institution's stained slides available for the local review of the biopsy and determine if any stained slides need to be sent to the DCC; if fewer than 2 unstained slides are available for sending to the DCC, the DCC must be sent the institution's stained slides
- If the DCC will be sent stained slides, label those stained slides with NASH CRN slide labels for stained slides (which are not the same as the labels for unstained slides); transcribe the slide sequence numbers (printed on the slide label) to form SD
- If the DCC will be sent stained slides, determine if CyNCh is borrowing the stained slides from the institution or if CyNCh is taking possession of the stained slides; if borrowing the stained slides, determine the date by which the slides need to be returned to the institution and note the source of the slides; record this information on form SD
- If unstained slides are obtained, label them with the NASH CRN slide labels for unstained slides (which are not the same as the labels for stained slides); transcribe the slide sequence numbers from the slide labels to form SD

The Study Pathologist should complete the Liver Biopsy Histology Worksheet (HW) form using the institution's H&E stained slide and Masson's trichrome stained slide, as described later in this document. The Clinical Coordinator will transcribe the data from the Histology Worksheet to the appropriate HF form. If the NAFLD activity score (NAS) is 3 or less the patient is ineligible for CyNCh, but may be eligible for the Pediatric Database 2 Study.

If there is no H&E stained slide or if there is no Masson's trichrome stained slide, the biopsy is insufficient for evaluation for entry into CyNCh.

If only the H&E and Masson's trichrome slides are available (i.e., no unstained slides available), these should be reviewed locally. If the patient is found to be eligible, these slides will need to be sent to the DCC for central review by the Pathology Committee. Both of these slides must be available for central review for the patient to be found eligible for CyNCh.

The CyNCh trial should request that the slides be provided outright, with no arrangements to return the slides at the end of the trial. In the event that any of the slides from a prior biopsy need to be returned to the original laboratory, the first plan should be for those slides to be returned at the end of the trial. If that is not acceptable to the original pathology laboratory, the slides will be returned to the original pathology laboratory after the central review is completed.

Slides for patients who are not randomized in CyNCh should be returned to the original pathology laboratory upon determination that the patient will not be randomized.

2.3. Baseline and followup biopsies performed after consent for screening - biopsy procedure

Each clinical center investigator will notify their CyNCh Study Pathologist (e.g., via local institutional requisition sheet) when a biopsy is performed on a CyNCh patient so that when the block is initially cut for the local institution's requirements, the CyNCh trial's additional 10 unstained slides can be cut at the same time. This will minimize the chances of loss of tissue with refacing the block.

In order to insure adequate material for histologic review, investigators should obtain needle core biopsies of at least 2.0 cm length using a 16 gauge or greater needle. If there is adequate tissue beyond 2.0 cm, the extra tissue may be stored in RNA*later*® Solution and banked at the Biosample Repository.

2.4. Preparation of slides

Biopsy tissue for slides should be placed in buffered formalin as soon as possible; investigators should use whatever formaldehyde solution is used by the site's pathology laboratory.

If this is a baseline biopsy, each clinical center will obtain locally stained H&E and Masson's trichrome slides as part of their standard institutional pathology materials; these will be read by the local CyNCh Study Pathologist for the local evaluation (i.e., for completion of form HW).

For both baseline and followup biopsies, the local laboratory should cut 10 additional slides (additional to what is cut for the institutional pathology needs) at the same time as the institutional slides are obtained in order to decrease the chances of loss of tissue with refacing the block. The local NASH CRN Study Pathologist should advise on the selection of a maximum of 10 unstained slides to be submitted to the Histology Review Center at the DCC for banking if there are (1) more than 10 unstained slides available or (2) if the unstained slides were cut from different tissue blocks obtained from the same liver biopsy core(s). The NASH CRN Pathology Committee's recommendation is that all unstained slides submitted come from the same, single liver biopsy core when possible. Centers should be careful not to submit unstained slides with insufficient or fragmented biopsy tissue since it is not possible for DCC staff to sort those out before sending the slides for central staining.

Tissue should be placed on pre-cleaned, "charged" slides to allow for possible future use with immunohistochemistry. The specifications for the recommended brand of slides are:

SuperFrost Plus slides, Precleaned
Distributor: Fisher Scientific
Catalog No.: #12-550-15
Size: 25/75/1.0 mm
Estimated cost: $133.07 per gross (144 slides/gross); $1,118.24 per case of 10 gross
Tele: 1-800-766-7000

Coverslips should not be placed on the slides. Slides should be labeled with the patient specific preprinted NASH CRN labels for unstained slides. The 10 (or as many that can be obtained up to 10) uncoverslipped, unstained slides will be forwarded to the DCC for the purposes of central staining, review, and archiving.

2.5. Labeling stained and unstained slides at the clinical center

Each of the slides (stained and unstained) sent to the DCC must be labeled with a NASH CRN slide label. Two types of slide labels are used in the NASH CRN:

(1) permanent labels are used for unstained slides; these labels can withstand the chemicals used during staining
(2) removable labels (overlabels) for stained slides that are borrowed from an institution.

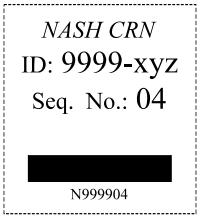
The requirements for the labeling scheme for slides are:

- Each slide must be uniquely identifiable
- The unique identifier for the slide has to be built from information that can be specified when the label is printed
- The slide label must be able to be read by human eyes
- Labels for unstained slides must be resistant to solvents used in the staining process and to over-labeling by interim processes (e.g., when sent for central staining)
- Labels for borrowed stained slides must be removable since those slides must be returned to the original pathology laboratory

The solution to these requirements is to use Brady labels in the format shown below: (1) labels for unstained slides and (2) labels for stained slides which are borrowed.

2.5. Labeling stained and unstained slides at the clinical center

(1)



(2)

Slide labels are provided to each clinical center in preprinted form, 1 set of labels per patient ID, by the DCC. Each set includes labels for unstained slides and labels for stained slides.

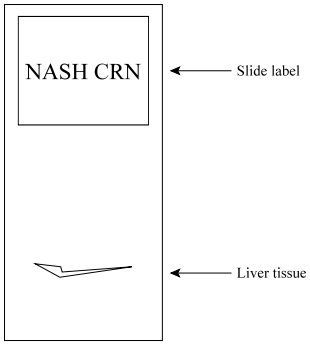
The unique identifier for a slide will consist of the patient ID number and a sequential number. The sequence numbers on the labels for unstained slides run from 01 to 60 (60 is the maximum number of unstained slides that we think we will ever get for any one patient over the life time of all NASH CRN studies). The sequence number on the labels for stained slides run from 81 to 90 (10 is the maximum number of stained slides that we think we will ever borrow for any one patient over the lifetime of all NASH CRN studies).

The slide labels include the following information:

- NASH CRN (printed on label)
- Patient ID number (4 digit number printed on label) and patient code (3 character alphabetic code printed on label)
- Slide sequence number (printed on label)
- Bar code constructed from N (for NASH CRN), 4 digit ID number, and 2 digit slide sequence number

Permanent labels should be positioned squarely at the top end of the slide, on the same side that the liver tissue is on and over the white part of the glass, with no edges hanging off the slide. Overlabels should be placed on the back of the slide, directly on the glass and opposite the existing

label. Both permanent labels and overlabels should be positioned so that the print is oriented vertically with the narrow end of the slide (see diagram below).



2.6. Liver tissue for banking at Biosample Repository

The extra piece of liver tissue (minimum 1-2 mm or greater) will be stored in RNA*later*® Solution as follows:

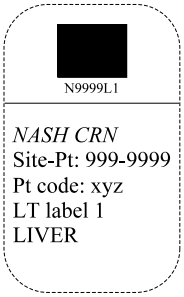
Labeling Procedures

- Apply pre-printed label provided by DCC to the cryogenic vial according to the following steps:

  - Attach the label to the vial when the vial is at room temperature
  - Leave the cap on the vial when labeling to ensure the inside of the vial remains sterile
  - Position the label on the vial so that the long edge of the label is parallel to the floor when the vial is held in an upright position; the label should not trail off the bottom of the vial or over the cap
  - While holding the vial in an upright position, affix the colored (white) portion of the label to the vial first
  - Wrap the clear tail around the perimeter of the vial; the end of the clear tail should overlap the colored portion of the label
  - Press firmly on the entire label; verify that all edges of the label adhere to the vial
  - When possible, allow newly labeled vials to set at room temperature for several hours prior to subjecting them to colder temperatures (24 - 48 hours is optimal)

2.6. Liver tissue for banking at Biosample Repository

- The liver vial labels have the following format:



- The vial used for banking extra liver tissue should be a 2.0 mL polypropylene cryogenic vial (13.5 mm wide x 48.3 mm tall) that is self-standing and externally threaded vials and silicone washers. This vial is designed for ultra low temperatures (-196 ° C, liquid nitrogen vapor) (supplier: CIC, catalog number 5012-0020; phone 877-738-8247)

- Preferably within one minute and no more than five minutes after biopsy, place the liver tissue into the vial, pre-filled with approximately 1 mL of RNA*later*® Solution. If the sample is not placed in RNA*later*® Solution within 5 minutes discard the sample. Refrigerate the cryovial at 4° C overnight to allow thorough penetration of the liver tissue and then transfer to -70° C freezer for storage.

- RNA*later*® Solution may be ordered online at http://www.ambion.com/catalog/catnum.php?AM7020. The catalog number for 100 mL of Ambion RNA*later*® Solution cat#AM7020 and sells for $96.

- Complete the Liver Tissue Banking (LT) form; the duplicate liver vial label should be attached to the LT form

- Make sure you use the "Cryovial" and "LT form" labels from the same set (i.e.., with the same sequence number)

- Complete the Specimen Shipment Log (SS) form. In the NASH CRN Excel shipment file under column J, enter "R"

- Batch ship cryovials to the NIDDK Central Biosample Repository on Monday, Tuesday or Wednesday; after refrigeration overnight at 4° C, store temporarily in -70° C freezer at the clinical center until the next batch shipment to Fisher Bioservices.

3. Development of the histology scoring system

3.1. Background

The NASH CRN has designed and validated a feature scoring system that can be used for the spectrum of NAFLD, both to correlate histologic features with clinical and physiologic measurements and to document changes in liver tissue observed over time in patients in natural history studies and clinical trials.

3.2. Methods and validation

Pathologists from the NIH and from the 8 clinical centers participating in the NASH CRN met in March 2002 to discuss the features to monitor and the criteria for scoring these features. Each study pathologist was asked to contribute cases of adult and pediatric liver biopsies. The cases were chosen from patients referred for consideration of NASH who had been histologically diagnosed as either diagnostic, borderline/suspicious, or not diagnostic of NASH. The cases were to have no confounding liver diseases. Subsequent to the March 2002 meeting and after criteria for the scoring system were established based on the discussions at the meeting, additional cases were requested from each center's pathologist. The original and newly received cases were anonymized and were assembled into what is called the anonymized study set. This set consists of 50 cases (32 adult, 18 pediatric) with H&E and Masson stains for each case.

During the summer and fall of 2002, the anonymized study set was circulated to each study pathologist for review to establish agreement for features and for diagnosis according to the three categories of definite, borderline, and not NASH. The adult cases were scored by each pathologist twice and the pediatric cases once.

Weighted group and pair-wise Kappa statistics were used to evaluate inter- and intra-rater agreement. Inter-observer agreement was assessed for both adult and pediatric cases and intra-observer agreement was determined using the adult cases.

Cochran's Chi-square test for trend and GEE logistic regression were used to analyze univariate and multivariate relationships between feature scores and the diagnosis of NASH. Adult cases were analyzed separately from pediatric cases.

3.2. Methods and validation

Fourteen features of NAFLD were evaluated in the scoring system. Four of the features were evaluated semi-quantitatively:

- Steatosis percent (0-3)
- Modified Brunt criteria for fibrosis (0-4); the modification, specifically, was subdivision of stage 1 into 1a, 1b, and 1c:
  - 1a: zone 3 perisinusoidal fibrosis that does not require a trichrome stain
  - 1b: zone 3 perisinusoidal fibrosis that does require a trichrome stain
  - 1c: portal fibrosis only

  The remainder of the fibrosis scoring used Brunt criteria.
- Lobular inflammatory foci/20x (0-3)
- Hepatocellular ballooning (0-2).

Location of steatosis was recorded but not scaled. An additional 9 features were recorded as either present or absent.

Weighted group kappa statistics for the inter-rater agreement on adult cases were 0.84 for fibrosis, 0.79 for steatosis, 0.56 for hepatocellular ballooning and 0.45 for lobular inflammation. Agreement on the diagnosis of NASH had a kappa of 0.61. Kappa values for intra-rater agreement were higher for all features, while inter-rater agreement on pediatric cases was generally lower. By multivariate analysis 5 features independently correlated with the diagnosis of NASH in adults: hepatocellular ballooning ($P<0.0001$), perisinusoidal fibrosis ($P=0.0009$), lobular inflammation ($P=0.002$), steatosis ($P=0.004$) and acidophil bodies ($P=0.02$).

In summary, we have devised a feature scoring system for NAFLD and NASH that has inter- and intra-rater agreement similar to other semiquantitative scoring systems for chronic liver disease. The pediatric NAFLD features were not as reproducible as those of adults, possibly due to the presence of varied patterns of injury. In accordance with the idea that NASH is a pattern of injury comprised of several features, this scoring system demonstrates that a firm diagnosis of NASH correlates with the degree of steatosis, characteristic pattern of fibrosis, lobular inflammation, and hepatocellular ballooning. Based on this evaluation, the NASH CRN will use this system to evaluate liver biopsies for features of NAFLD.

4. Evaluation at the clinical center (for forms HW and HF)

4.1. Introduction

The local site CyNCh Study Pathologist will evaluate baseline biopsies only, for eligibility determination only. CyNCh patients must have histologically confirmed NAFLD with a NAS ≥4.

The local site CyNCh Study Pathologist should make his/her evaluation using the locally stained H&E slide (all features except fibrosis) and Masson's trichrome slide (fibrosis only) and should complete the Liver Biopsy Histology Worksheet (HW) form. The information on the HW form will be transcribed to the study-specific HF form by the clinical coordinator. A copy of the HF and HW forms are included at the end of this document for your information; please obtain blank forms for completion for a patient from the study website (https://jhuccs1.us/nash) or from the Clinical Coordinator.

4.2. Guidelines for features scored in the local evaluation

The following guidelines are provided for uniformity of reading among the CyNCh pathologists. The system is based entirely on H&E stain for all lesions except fibrosis, and on Masson's trichrome stain for fibrosis.

4.2.1. Length of biopsy

The tissue is measured (mm) on the glass slide prior to reading the slide.

4.2.2. Steatosis grade (0-3; 4x or 10x)

0: <5%
1: 5 -33%
2: 34 - 66%
3: > 66%

In the recognition that (1) deciding on less than 5% can be challenging and (2) that this really is a significant cut-off for allowing patients into long-term follow-up studies such as the NASH CRN is conducting, we think it is best to err on the side of grade 1 rather than grade 0 when faced with a borderline case. Evaluation is best at 4x or 10x at most.

4.2.3. Steatosis location

Steatosis location has 4 choices for characterization:

Zone 3: distribution means not panacinar and not strictly zone 1
Zone 1
Azonal: this pattern is the random scattered macrosteatosis
Panacinar: implies severe steatosis that appears to involve the whole acinus equally, rather than the more random azonal pattern

4.2.4. Fibrosis stage (0-4; requires Masson's trichrome slide)

0: None
1a: Zone 3, perisinusoidal fibrosis (requires trichrome)
1b: Zone 3, perisinusoidal (easily seen on H&E; verified on trichrome)
1c: Portal/periportal only
2: Zone 3 and periportal, any combination
3: Bridging
4: Cirrhosis

4.2.5. Portal chronic inflammation (0-1)

0: None to minimal
1: Mild
2: More than mild

4.2.6. Lobular inflammation (0-3; 20x)

Amount of lobular inflammation combines mononuclear, fat granulomas, and polymorphonuclear (pmn) foci.

0: None
1: < 2 / 20x mag
2: 2-4 / 20x mag
3: >4 / 20x mag

4.2.7. Hepatocellular ballooning (0-2)

0: None
1: Few
2: Many

4.2.8. Steatohepatitis diagnosis

At some point in your evaluation of the case, decide how you would sign this case at your institution, using whatever criteria you currently use to make a diagnosis of steatohepatitis. The question asked is "Is steatohepatitis present?" and the choices for response are:

0: Not NAFLD
1: NAFLD, but not NASH
2: Suspicious, Zone 3 pattern (1A)
3: Suspicious, Zone 1 pattern (1B)
4: Yes, definite steatohepatitis

This choice has to be made based on the H&E and Masson's trichrome slides, even if you have access to other stains (such as ubiquitin immunohistochemistry).

4.2.9. Exclusion of other liver disease and other features

- Primary biliary cirrhosis
- Wilson's disease
- Chronic cholestatic liver disease
- Inflammation suggestive of AIH, HCV
- Pigment suggestive of HH
- Globules suggestive of A1AT
- Hepatocellular changes suggestive of HBV
- Granulomas suggestive of sarcoid, PBC, infection

Diagnosis of primary biliary cirrhosis, Wilson's disease, bile duct obstructions, primary sclerosing cholangitis, autoimmune liver disease, HCV, hemochromatosis, A1AT deficiency, and HBV by the study physician are exclusionary; these diagnoses are marked with Caution symbols on the HF form.

4.2.10. NAFLD Activity Score (NAS)

The NAFLD Activity Score (NAS) is a composite score that is calculated from the steatosis grade (0-3), the lobular inflammation grade (0-3), and the hepatocellular ballooning score (0-2); the scores for these three components are summed. The NAS may range from 0 through 8. Patients with

a NAS of 0-3 on screening are ineligible for CyNCh, but may be considered for the Pediatric Database 2 Study.

4.2.11. Comments

This item is for any comments you want to share with the rest of the group on the case such as comments on unusual features or on a difficult scoring choice.

4.3. Unscheduled liver biopsy

Unscheduled biopsies (i.e., biopsies done after screening and at a followup time other than 52 weeks after randomization) will be evaluated locally for standard of care and also centrally by the Pathology Committee. Forms HW and HF will not be completed for unscheduled liver biopsies, but the biopsy slides should be obtained and the SD form should be completed. Form CR will be completed upon central review by the Pathology Committee. The CR form will use visit code n or the visit code for the visit that was open when the biopsy was obtained.

5. Central pathology evaluation (for Form CR)

5.1. Procedures

Each pathology review session will include attendance by at least three Pathology Committee members and will include at least one of the co-chairs. Central reviews are planned for every 3-4 months. Review sessions will last 1 - 2 days. One or two DCC members will attend each central review to complete the Central Pathology Review (CR) form for each biopsy reviewed. These completed data forms will be keyed at the DCC.

Following central review, slides will be returned to storage at the DCC. Slides that are only loaned to the CyNCh trial for a specified time will be returned to the clinical center at the required time. Slides will be packed and shipped for return to the clinical center as specified later in this manual.

5.2. Documentation of which slides were used for evaluation

The sequence numbers of the slides viewed will be recorded on the CR form for each case.

5.3. Guidelines for features scored in the central evaluation

The following features are evaluated both centrally and locally, and the guidelines to be used for the central evaluation of these features are the same as the guidelines used for the local evaluation:

- Steatosis grade
- Steatosis location
- Fibrosis stage
- Lobular inflammation
- Portal chronic inflammation
- Hepatocellular ballooning
- Cirrhosis diagnosis
- Steatohepatitis

Steatohepatitis diagnosis and amount of portal inflammation are scored both centrally and locally, but the scoring of these features for the central evaluation differs from the scoring for the local evaluation.

Guidelines for features scored only in the central evaluation or scored differently in the central evaluation from the local evaluation are described below.

5.3 Guidelines for features scored in the central evaluation

5.3.1. Steatosis

5.3.2a Types of Macrovesicular steatosis

0: Predominantly large droplet macrovesicular steatosis
1: Mixed large and small droplet macrovesicular steatosis
2: Predominantly small droplet macrovesicular steatosis

5.3.2b Microvesicular steatosis, continguous patches

0: Absent
1: Present

The definition agreed on was the pathologists' definition of microsteatosis: foamy appearance to the cytoplasm, nucleus centrally located. Remember, this is not the small droplet type of "macro" steatosis that does not completely fill the cell. Microsteatosis typically needs ORO for confirmation in routine practice.

5.3.2. Microgranulomas seen (yes/no)

5.3.3. Large lipogranulomas seen (yes/no)

5.3.4. Ballooning

5.3.4a: Severe ballooning present

0: No
1: Yes

A score of "severe ballooning present" should be made if large, classical balloon cells are seen from low magnification in multiple areas throughout the biopsy. The biopsy should already have a score of "2" for ballooning to qualify for severe ballooning.

5.3.4b: Classical balloon cells present

0: No
1: Yes

Classical balloon cells are ones that are easily recognized at low to medium magnification, stand out from the surrounding parenchyma and have cytoplasm that is clumped. They may have Mallory-Denk bodies. A positive score requires only one classical balloon cell.

5.3.5. Pigmented macrophages (Kupffer cells)

0: Rare/absent
1: Many

5.3.6. Megamitochondria

0: Rare/absent
1: Many

5.3.7. Mallory - Denk bodies

0: Rare/absent
1: Many

5.3.8. Glyogen nuclei

0: Rare/absent
1: Present in patches

5.3.9. Glycogenosis of hepatocytes

0: Not present
1: Focal, involving less than 50% of the hepatocytes
2: Diffuse, involving more than 50% of the hepatocytes

5.3.10. Fibrosis

5.3.10a: Perisinusoidal fibrosis grade

0: No perisinusoidal fibrosis present
1: Perisinusoidal fibrosis present that requires a Masson stain to identify
2: Perisinusoidal fibrosis present that is visible on the H&E stain

Note that stage 1A fibrosis would automatically get a score of 1 and stage 1B fibrosis would automatically get a score of 2 on this scale.

5.3.10b: Predominant location of fibrosis (scored only if fibrosis stage is 1A, 1B, 1C, 2 or 3)

0: Fibrosis is more prominent around or between portal areas
1: No portal or central predominance to the fibrosis
2: Fibrosis is more prominent around or between central veins

Note that stage 1A and 1B fibrosis would automatically get a score of 2 and stage 1C fibrosis would automatically get a score of 0 on this scale.

5.3.11. Iron: hepatocellular grade (0-4)

0: Absent or barely discernible, 40x (skip hepatocellular iron distribution)
1: Barely discernible granules, 20x
2: Discrete granules resolved, 10x
3: Discrete granules resolved, 4x
4: Masses visible by naked eye

5.3.12. Iron: hepatocellular distribution

0: Periportal
1: Periportal and midzonal
2: Panacinar
3: Zone 3 or nonzonal

5.3.13. Nonhepatocellular iron grade (0-2)

0: None (skip nonhepatocellular iron distribution)
1: Mild
2: More than mild

5.3 Guidelines for features scored in the central evaluation

5.3.14. 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

5.3.15. Comments

General comments on the biopsy can be recorded by the Pathology Committee.

6. Shipping slides to the Data Coordinating Center

6.1. Packing and shipping slides

The steps in shipping slides to the Data Coordinating Center are:

- Complete the Histology Slide Transmittal Log (Form TS), specifying the number of stained and unstained slides for each patient included in the shipment; specify the date and visit code for the slides for each patient included in the shipment; make a copy of the completed TS form for your clinic records and include the original in the shipment
- Attach a copy of the surgical pathology report for each slide set included in the shipment; make sure that each report is annotated with the patient's NASH CRN ID number and ID code and that the patient's name has been blacked out
- Packing
  - Pack slides in standard slide shipping boxes, which hold 25 slides (VWR International catalog number 82003-418, HS15989A (blue), 82003-420 (green); phone 800-932-5000)
  - Use tissue paper or something similar, inside the box, to prevent the slides from moving during shipment
  - Seal the box shut with tape
  - Wrap the box in bubble wrap
  - Place the bubble wrapped box inside a padded jiffy bag. Place the jiffy box and pathology reports and Form TS in a Federal Express box; stuff the Federal Express box as needed with newspaper or other packing material so that the bubble wrapped box does not move around
  - Ship second day arrival to:

    Pat Belt
    NASH CRN Data Coordinating Center
    615 North Wolfe Street, Room W5010
    Baltimore, MD 21205
    410-614-6021

    You may bill the shipment to the DCC's slide shipment Federal Express account (#2991-6250-8)
  - Notify Pat Belt to expect the shipment (email pbelt@jhsph.edu or fax 410-955-0932)

6.2. Receipt of slides at the Data Coordinating Center

When slides are received, staff at the Data Coordinating Center will:

- Notify the clinic that the shipment was received
- Review the shipment for consistency with the accompanying shipping log, for damage, for appropriate labeling and other quality control items
- Log the slides into the DCC slide inventory system and designate a storage location
- Send slides for central staining as appropriate (currently, 3 stains are planned)
- If the received slides are not adequate for evaluation, the institution's slides may be requested and used to evaluate a biopsy

6.3. Returning slides to the clinical center

- Log the slides out of the DCC slide inventory system
- Complete a shipping log for return of slides to the clinical center
- Pack up slides for return to the clinical center
- Notify the clinical center of the impending return of the slides
- Obtain confirmation of receipt of the returned slides from the clinical center

7. Appendices

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7.1. CR- Central Histology Review

1	[2 page insert]

2

7.2. HW - Liver Biopsy Histology Worksheet

1	[3 page insert]

2

7.2. HW- Liver Biopsy Histology Worksheet

3

7.3. HF - Liver Biopsy Histology Findings

1	[3 page insert]

2

3

7.4. LT - Liver Tissue Banking

1	[2 page insert]

2

7.5. SD - Liver Biopsy Materials Documentation

1	[3 page insert]

2

7.5. SD - Liver Biopsy Materials Documentation

3

7.6. SS - Specimen Shipment Log

1	[2 page insert]

7.6. SS - Specimen Shipment Log

2

7.7. TS - Histology Slide Transmittal Log

1	[2 page insert]

7.7. TS - Histology Slide Transmittal Log

2

NASH CRN

Nonalcoholic Steatohepatitis Clinical Research Network

CyNCh

Standard Operating Procedures

Part V

Standard of Care for Children with Fatty Liver Disorders

November 2012

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1. Introduction

The purpose of this document is to articulate a uniform set of practices to be applied by investigators in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) to the care of pediatric patients with fatty liver disorders. As directed by the NASH CRN Steering Committee, these standards were developed so that pediatric patients with fatty liver disorders will receive uniform treatment across study sites, thereby reducing the extent to which care at a particular site will independently influence outcomes. These standards of care were derived by expert opinion, specifically the opinions of the NASH CRN investigators, and as such cannot and should not be construed to mean that they should be applied outside of the NASH CRN clinical centers or that the failure to apply these standards is a breach of community standards of care.

The NASH CRN Standards of Care Committee developed these standards in their initial draft form after the first meeting of the Committee on July 29, 2002 in Baltimore, MD. After review and revision, it was submitted to the NASH CRN Steering Committee and approved in principal at its meeting on September 22, 2002 in Atlanta, GA. The document was revised for the continuation of the NASH CRN in 2009 and approved by the Steering Committee in 2009. Committee members are aware that application of the standards described here could be viewed as an intervention in itself. However, the committee also felt that these standards are essential to fulfill our obligation to provide the best care to the participating pediatric patients.

2. Specific recommendations

2.1. Evaluation of patients with suspected NASH

a. Obtain the following**:**
   i. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), fasting lipid profile, insulin and glucose
   ii. Alpha-1-antitrypsin (A1AT) level, ceruloplasmin, and hepatitis B and C panels will be obtained. Auto-antibody studies for autoimmune hepatitis (AIH), antinuclear antibody (ANA), antismooth muscle antibody (ASMA), and antibody to liver-kidney microsomal antigen (anti-LKM1) may be drawn at the discretion of the study physician.
   iii. Imaging study (ultrasound, CT scan, or magnetic resonance image) to evaluate fat in the liver

b. Liver biopsy can be considered in patients with suspected NAFLD to confirm the diagnosis and stage the degree of injury. Imaging and degree of abnormality in serum aminotransferases may suggest the diagnosis but may not reflect the degree of injury or establish diagnosis

2.2. Dietary intake

a. A “heart healthy”, Choose My Plate (www.choosemyplate.gov, United States Department of Agriculture) diet will be recommended to patients. Health and Nutrition Information for children over five is available at www.choosemyplate.gov/children-over-five.html. Specific recommendations may include:
   i. Less than 30% of calories from fat
   ii. Less than 10% from saturated fats by selecting non-fat dairy products such as milk, yogurt, cheese, fish or poultry without skin, and preparing food with small amounts of unsaturated oils such as olive and canola oils.

iii. Eat foods free of commercial trans fatty acids
iv. Fill half the plate with fruits and vegetables of different colors to consume at least five servings of fruits and vegetables per day.
v. If subject is overweight, then modest total calorie restriction, calculated from expected needs based on height and age, with weight loss goal of 1-4 pounds per month.
vi. Patient's diet must meet recommended dietary allowances (RDAs) for micronutrients including calcium and Vitamin D.

b. Patients with known or newly discovered type 2 diabetes will receive specific recommendations as promulgated by the American Diabetes Association (ADA).
c. Recommendations regarding the use of specific nutritional supplements are addressed below.
d. Dietary recommendations may not apply to all persons or situations.

2.3. Weight loss

a. Weight loss recommendations will be individualized. Very overweight subjects (BMI ≥ 95%) may be given a target goal of losing and sustaining the loss of 10% of body weight or down to BMI< 85%. This weight loss target may be achieved at a rate of 2 - 4 pounds per month per expert committee recommendations.
b. Food guide pyramid and other age-appropriate materials will be used as instructional material.
c. Patients will be instructed not to fast as a means of achieving weight loss.
d. Alternative diet plans will not be recommended.
e. Family education regarding healthy eating, fast food, etc. will take place. Educational materials on parenting skills and obesity will be developed.

2.4. Alcohol consumption

a. Pediatric patients will be reminded that alcohol consumption is prohibited.

2.5. Exercise

a. Patients will be instructed to engage in moderate to vigorous exercise for a minimum of 60 minutes or more daily. This will be defined as continuous physical exertion sufficient to raise the heart rate to 130 and "break a sweat." Patients/families will be advised to limit TV-watching and video/ computer game time to less than 2 hours per day. Further recommendations can be found at: http://www.cdc.gov/physicalactivity/everyone/guidelines/children.html

2.6. Preventive medicine

a. **Vaccination for viral hepatitis**. Hepatitis B vaccine is standard of care for children. While hepatitis A vaccine is now routine, many teenagers may not have undergone vaccination yet; these teens with underlying liver disease should receive the hepatitis A vaccine. Compliance will not be monitored for the study since disparities in clinical center practices would have no impact on the studies of the NASH CRN.
b. **Hepatocellular carcinoma screening**. Although recent data suggest that cirrhosis caused by NASH is associated with a similar risk of developing hepatocellular carcinoma as other major causes of cirrhosis, there is lack of consensus in the field regarding an optimal cost-effective screening strategy, particularly in pediatrics. Screening methods will not be standardized across sites, but will be in accordance with local standards.

2.7. Management of coexisting morbidities

a. **Type 2 diabetes**

i. Some patients will not have a pre-existing diagnosis of type 2 diabetes but meet diagnostic criteria as a result of testing performed for NASH CRN studies. These patients will be referred to a pediatric endocrinologist for appropriate management.

ii. Patients with controlled diabetes (hemoglobin A1C < 7%) will be continued on their current treatment regimens.

iii. Patients with suboptimally controlled diabetes (hemoglobin A1C > 7%) will receive a recommendation for follow-up with their pediatric endocrinologist for improved glycemic control.

b. **Hypertriglyceridemia**

For patients with fasting triglycerides > 150, referral to a dietician should be considered For patients with triglycerides > 250 further evaluation should be considered.

c. **Hypercholesterolemia**

Patients with fasting total cholesterol levels > 200 mg/dL will be referred to a dietitian for step 1 diet (NCEP) and those with a total cholesterol > 220 or low-density lipoprotein (LDL) cholesterol of ≥ 130 should be further evaluated. Treatment should be considered for LDL cholesterol levels ≥ 160 if risk factors such as a family history of early heart disease or diabetes is present, or LDL cholesterol levels ≥ 190 if no risk factors are present. Study physicians may refer patients to a lipid specialist at their discretion. Further recommendations can be found at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics;122/1/198#SEC5

d. **Hypertension**

For patients with repeated systolic blood pressure or diastolic blood pressure > 95% for age and height (NHLBI), referral for further evaluation should be considered.

e. **Sleep apnea**

Symptoms suggestive of sleep apnea (snoring, observed periods of apnea, disruptive sleep disturbances) will be specifically sought as part of the review of symptoms. If these symptoms are present, patients will be referred for a possible sleep study. The rationale for this assessment is that disrupted sleep will contribute to fatigue and the role of periods of hypoxia in the pathogenesis of liver injury is unknown.

f. **Hyperandrogenism and polycystic ovary syndrome (PCOS)**

Girls with hirsutism (facial and/or chest hair) and menstrual irregularities not associated with prepubescence will be referred to the appropriate specialist.

g. **Occupational exposure to hepatotoxins, recreational drugs, etc.**

A history of ongoing exposure to volatile hydrocarbons or recreational drugs will be sought. All subjects with positive histories will be cautioned regarding dangers of use and instructed to avoid/stop usage.

h. Evaluation of pediatric NASH patients with age < 5 years or developmental delay will include urine organic acids (and perhaps other metabolic testing) to evaluate for underlying metabolic disease.

2.8. Possibly helpful concomitant medication use

a. Vitamin E
   i. Patients receiving a stable dose of Vitamin e for at least 6 months may continue use of Vitamin E.
   ii. For therapeutic trials, Vitamin E may not be initiated in the time period between liver biopsy and randomization.
   iii. For therapeutic trials, if a patient is taking Vitamin E but adherence is poor, Vitamin E may be stopped.

b. Ursodeoxycholic acid (UDCA, Actigall, Urso, Ursodiol)
   i. UDCA will generally be stopped unless new data is published to indicate a significant benefit for patients with NASH.
   ii. UDCA will be continued in patients who have shown a significant improvement associated with treatment in liver histology or surrogate markers for NAFL such as ALT or imaging studies. 90 day UCDA washout may be required before therapy studies.

c. Metformin
   i. Patients receiving metformin as a treatment for diabetes will remain on the drug.
   ii. Patients receiving metformin as a treatment of other disorders of insulin resistance (e.g., PCOS) will remain on the drug.
   iii. For therapeutic trials, if a patient is taking Vitamin E but adherence is poor, Vitamin E may be stopped.

d. Fibrates: There is little experience in children. Use will be decided on an individual case basis in children with hypertriglyceridemia.

e. Statins: There is little experience in children. Use will be decided on an individual case basis in children with hypercholesterolemia.

f. Thiazolidinediones (TZDs; pioglitazone, rosiglitazone)
   i. Patients receiving a TZD as a treatment for diabetes will remain on the drug.

2.9. Possibly harmful concomitant medication use

a. Acetaminophen
   i. Acetaminophen should be restricted to < 45 mg/kg/d in any given day.
   ii. Repeated use of > 20 mg/kg daily for more than 3 consecutive days should be discouraged.
   iii. Families should be warned that many over-the-counter (OTC) medications contain acetaminophen. Labels should be read carefully.

b. Anticonvulsants: Children with seizure disorder will continue on previous anticonvulsants. Neurologists treating children with NASH with Valproate will be asked to change to a different anticonvulsant if possible.
   i. Valproate washout may be required before therapy studies.

c. Estrogens (oral contraception, hormone replacement therapy)
   i. Estrogen use as oral contraception will be permitted.

d. Iron supplements
   i. Patients with iron deficiency will be allowed to continue the use of iron supplements until iron stores are sufficient. In the case of ongoing blood loss (e.g., meno/metrorrhagia, refractory GERD, portal hypertensive gastropathy), iron supplements will be continued as long as the transferrin saturation remains < 50%.
   ii. Patients having normal iron status (serum ferritin > 15 ng/mL or transferrin saturation > 20%) and taking iron supplements will be requested to discontinue the supplements.

e. Accutane
    i. Accutane may cause elevations in liver enzymes as well as lipids. In the context of NASH, this drug should be discontinued.
f. Prednisone
    i. Use should be minimized.

2.10. Possibly helpful concomitant dietary supplement use

a. Multivitamins. A daily multivitamin with iron content < 20 mg daily will be allowed.
b. Betaine. Betaine should not be used outside of a trial. 90 day betaine washout may be required before therapy studies.
c. S-adenosylmethionine. SAM should not be used outside of a trial. 90 day SAM washout may be required before therapy studies.
d. Creatine and other bodybuilding supplements will be forbidden.

2.11. Possibly harmful concomitant dietary supplement use

a. Vitamin A supplements in excess of that contained in a daily multiple vitamin (5000 IU) should not be used.
b. Herbal supplements.
    i. For therapeutic trials, herbals may not be initiated in the time period between liver biopsy and randomization.
    ii. If a herbal supplement is believed to be hepatotoxic, then use of that supplement should be discontinued.

3. Implementation

The intention of the NASH CRN is to implement these standards of care immediately in the patients followed at all clinical centers. There will be no standardized lead-in period during which these standards will be applied before patients are enrolled in NASH CRN studies. Implementing the standards in patients with only steatosis on a liver biopsy will be at the discretion of the hepatologist. The committee believes that implementing these standards of care constitutes good clinical practice and does not constitute an intervention; moreover, data will not be collected regarding outcomes after implementation of these standards. As such, their implementation is not under the purview of local Institutional Review Boards.

Responsibility for implementation. The NASH CRN will develop uniform teaching materials to provide patients with the information detailed above. Clinical centers will be responsible for printing costs. The materials will be distributed to patients by their hepatologists or other health care worker such as nurses and nutritionists. Distribution of materials to patients will be documented in their medical records.

Compliance and reinforcement. Patients' adherence to the above guidelines will be established by the study personnel. The practices will be reviewed by the hepatologist or associated health care worker with the patient during the clinic visit. Patients will be given the opportunity to take the teaching materials outlining the above recommendations at each hepatology clinic visit.

Frequency of follow-up. Patients will be seen at least once yearly by the hepatologist. The visit should include an interim history, review of symptoms, updated medication list, physical exam, lab work, and discussion of adherence to the standard of care recommendations.

4. Preparation and dissemination of materials needed to implement the standard of care

4.1. Physician summary of guidelines

a. Physicians at the study sites will need ongoing reminders of the specifics of the standards of care.
b. Perhaps a pocket card and a small poster for patient care areas are needed.

4.2. Patient brochures

a. What brochures are needed:
    i. Healthy eating
    ii. Healthy weight loss
        (1) BMI formula and curves
        (2) Goals
    iii. Handout on parenting skills (See Section 5.1)
    iv. General NASH brochure to cover most other recommendations
        (1) Acetaminophen use
            a. Allowable amounts
            b. List of medications
        (2) Supplemental iron use
        (3) Vitamins
            a. Allowable vitamin A
            b. MVI daily
        (4) Warning about herbal remedies
        (5) Symptoms to report
            a. Sleep apnea
            b. Irregular menstruation, facial hair
b. Brochure development
        i. Content: Standard of Care Committee (See Section 5.2)
        ii. Design: Need a professional aesthetically pleasing design
        iii. Printing: Local center to arrange for printing, distribution, cost recovery
c. Updates to the brochures
        i. Content to be reviewed annually and discussed at Steering Committee meetings
        ii. Revised content and design to be prepared within 4 weeks of review at Steering Committee. Revisions to be distributed to the Steering Committee members for final approval.

4.3. Referring physician information

a. Implementation of the standard of care will occasionally require communication of findings such as newly diagnosed diabetes, hypertension or hyperlipidemia. This communication should be made according to local protocol and physician judgment. Documentation of referrals should be kept in the patient's NASH CRN file.

4.4. Website

A public website will be considered in the future, but will not be implemented during the first year of the trial.

5. Parent guidelines and patient brochure

Printable versions of the Parent Guidelines and Patient Brochure are available on the NASH CRN website: http://www.jhuccs1.us/nash/closed/cped/CYNCH/sop.htm. If you print the guidelines or brochure from the SOP, the headers and footers will cause the documents to not fit the page correctly; therefore, you must go to the website to print the documents.

5.1. Lifestyle intervention approach in the CyNCh trial

Attaining a healthy weight is the cornerstone of our current treatment of pediatric nonalcoholic fatty liver disease (NAFLD), given the lack of proven pharmaceutical therapy in this age group and the strong association of NAFLD with excess adiposity, in particular central adiposity.(1) Weight loss has been associated with improvements in liver enzymes and histology in adults with NAFLD, while weight loss in children with NAFLD has been shown to improve serum aminotransferase levels in small pilot studies.(2-4) Therefore, lifestyle intervention through changes in diet and exercise will be encouraged for participants in both the placebo and intervention arm of the CyNCh trial, as this represent the current standard of care for this disease in children.

The standard of care lifestyle intervention designed for this trial will incorporate components of the American Academy of Pediatrics' 2007 Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity that can be reproduced across the study sites.(5) CyNCh study participants will be given a study-specific set of written materials that will include discrete evidence-based strategies to achieve a healthier diet and increase physical activity, as endorsed by the American Academy of Pediatrics as well as the CDC and NIH.(5-7) A family-based, patient-centered and stepped approach to making lifestyle changes will be employed as recommended by the AAP.(5) Accordingly, the lifestyle materials will be reviewed with study participants and their family members at each study visit (RZ, F4, F12, F24, F36).

Topics to be covered in the materials will include:

RZ VISIT: 1) Reduce fat intake and sugar intake to 0 servings per day of sweets.
F4 VISIT: 2) Reduce screen time to 2 hours or less per day
F12 VISIT: 3) Increase physical activity to 1 hour or more per day
F24 VISIT: 4) Increase fruits and vegetable intake to 5 or more servings per day
F36 VISIT: 5) Make healthier choices when eating out

These topics and the specific strategies to be included in the lifestyle intervention materials are in accordance with healthy weight strategies currently recommended by the Centers for Disease Control and the National Institutes of Health National Heart Lung and Blood Institute's "We Can" program.(6-8) Therefore, we will also include references in the study's lifestyle intervention materials to these freely accessible, federal government sponsored websites so that participants and their families can easily access additional information on these lifestyle changes and strategies to achieve them.

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6) http://www.cdc.gov/healthyweight/children/, accessed September 22, 2010
7) http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/index.htm, accessed September 22, 2010
8) http://www.fruitsandveggiesmatter.gov/ accessed September 22, 2010

NASH CRN CYNCH Trial

Achieving a healthy weight can improve fatty liver disease

TIP # 1: REDUCE SWEETENED FOODS AND BEVERAGES– AIM FOR 0 SERVINGS PER DAY ON MOST OR ALL DAYS OF THE WEEK.

Limiting fat and sugar intake can help you achieve a healthy weight. Many prepared foods and drinks have added sugars, both table sugar and high fructose corn syrup. Both types of sweeteners can contribute to unwanted weight gain and make fatty liver disease worse. Sugar is found naturally in some foods, like fructose in fresh or dried fruits or lactose in milk. The grams of sugar in these foods are too small to worry about unless you eat or drink these foods in very large amounts.

Saturated fats (fats that tend to be solid at room temperature, like butter and whole fat milk) can promote weight gain. Foods with saturated fats or made with saturated fats are typically higher in calories per serving.

Beware of foods that are labeled fat-free or reduced fat. Many of these prepared foods have added sugars and the same number of calories as regular food. The easiest way to reduce fat and sugar intake is to eat foods that are not processed. Choose foods that you prepare yourself from raw ingredients.

Here are some ideas on how you can avoid added sugars and saturated or trans fats:

1) Avoid beverages or sodas sweetened with sugar. Choose water rather than fruit juice or soda. Choose diet drinks if you must drink a soda.
2) Choose low fat dairy products (skim milk, low fat milk or cheese products) for cooking or snacks. For example, use part skim mozzarella cheese in lasagna.
3) Read labels and avoid foods that contain saturated or trans-fats.
4) If you love sweets, limit your intake of cookies or sweets to 1 or 2 days per week and stick to 1 serving.
5) Choose fresh or frozen fruit with low fat unsweetened yogurt for dessert.
6) Limit your fast food intake to no more than one time per week or once every other week. Most fast food choices are loaded with added sugar, salt and fat.

For more information visit:
http://www.choosemyplate.gov/food-groups/downloads/TenTips/DGtipsheet13CutBackonSweetTreats.pdf
In Spanish: http://www.choosemyplate.gov/downloads/DGTipSheet13CutBackonSweetTreats-sp.pdf
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/index.htm
http://www.choosemyplate.gov/physical-activity.html

TIP #2: CUT DOWN ON SCREEN TIME TO 2 HOURS OR LESS PER DAY

Reduce your "screen time" – this is the total time you spend watching TV, DVDs, playing video games, texting or using a phone or the computer for *anything* other than school or work.

- It's important for the whole family, including parents and kids, to sit less and move more to have more energy, learn new skills and be at a healthy weight.
- Be a good role model. Parents *and* kids should limit screen time to no more than 2 hours per day.
- Don't use TV or video game time as reward or punishment.

Here are some ideas on how to cut down your family's screen time:

1. Keep track of how much time you and your family spend in front of a screen (TV, computer or phone) and how many hours you spend being active (walking, active playing, gardening, swimming, running) on a weekly or monthly calendar. Have a family competition to see who can increase their active time and decrease their screen time the most in one month!
2. When you do spend time in front of a TV or computer, take breaks to be active. During commercial breaks, get up stretch, walk around the house, do yoga, leg lifts, or lift weights. Compete with your family members to see who can do the most jumping jacks or sit ups during breaks.
3. Move TVs out of your bedrooms.
4. Make meal times about family time and turn off the TV.
5. Set a house rule on the amount of TV and screen time per day at home and stick with it! Remember your goal of no more than 2 hours of screen time per day.
6. Go for a half hour walk or any other physical activity instead of watching TV.

For more information, visit:
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/reduce-screen-time/tips-to-reduce-screen-time.htm

TIP # 3: INCREASE YOUR PHYSICAL ACTIVITY TO 1 HOUR OR MORE PER DAY

Getting more active can boost your energy, cardiovascular fitness, help you achieve a healthy weight and reduce the fat around your middle and in your liver.
Start with small steps to get more active every day: Choose a different tip each week to gradually increase your daily activity.

Here are some ideas on how you can get more active:

1. Walk to nearby destinations or friends' houses instead of driving whenever possible.
2. Walk to school if you can.
3. Take the stairs instead of the elevator or escalator at school, work or when out.
4. Take a daily family walk together after dinner or make a weekend walk a family habit.
5. Get off the bus one stop early and walk to your destination.
6. Park further away from the store or mall to get in a little extra walking while shopping.

7. Take your dog on longer walks.
8. Play outside for at least 30 minutes 2 times per day to achieve your goal of 1 hour.
9. Dance to music or a music DVD at home instead of watching a TV or cable show.
10. Help around the house: wash the car, work in the yard, clean your room, and help with laundry.

For more information visit:
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/get-active/getting-active.htm
http://www.choosemyplate.gov/physical-activity.html

TIP #4: FRUITS AND VEGETABLES MATTER – AIM FOR 5 A DAY

- Use MyPlate (www.choosemyplate.gov/food-groups) to determine how many servings of fruits and vegetables you should eat each day.
- Choose fresh, frozen or canned fruits and vegetables
- Rinse canned products because of the added salt and sugar

Here are some ideas on how to add more fruits and vegetables to your meals and snacks:

1. Blend a fruit smoothie using your favorite fruits and low fat milk or yogurt.
2. Add extra fresh, frozen or canned chopped vegetables to your family's favorite recipes.
3. Add extra vegetables to salads – grated carrots, sliced cucumbers, cherry tomatoes.
4. Choose sliced fruit for breakfast on your cereal, whole grain waffle or pancake.
5. Pre –plan by packing a school lunch the night before – add a serving of fruit or vegetable.
6. Keep ready-to-grab healthy snacks in your kitchen – veggies rinsed and cut up in the refrigerator, and apples, banana, and grapes ready to wash and eat.
7. Put fresh fruit such as melon chunks in the freezer for a frozen treat.

For more ideas and information visit:
http://www.choosemyplate.gov/food-groups/downloads/TenTips/DGTipsheet11kidfriendlyveggiesandfruits.pdf
In Spanish: http://www.choosemyplate.gov/downloads/DGTipSheet11kidfriendlyveggiesandfruits-sp.pdf
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/index.htm
http://www.cdc.gov/healthyweight/children/
http://www.fruitsandveggiesmatter.gov/

TIP# 5: MAKE HEALTHY CHOICES WHEN EATING OUT OR ORDERING TAKE OUT FOOD.

Foods cooked in restaurants or fast food chains are often loaded with sugar, fat and salt.
It is more challenging to eat well and stay healthy if you eat out more than one time per week.

Your best strategy is to reduce the number of times you eat out to no more than one time per week. Here are some ideas on how to make healthier choices and reduce your intake of sugar and fat when you choose to eat out or order carry out food.

Here are some ideas on how you can make healthier choices when eating out or taking out food:
1) Choose items from the menu that are steamed, broiled, baked, roasted, or poached.
2) Ask for low fat salad dressing on the side and use no more than 1 tablespoon.
3) Limit high calorie toppings (dried fruit, croutons, bacon bits) on your salad to 1 tablespoon.
4) Ask the waiter to leave out the gravy or sauce on your entrée or sandwich
5) Choose fruits or steamed vegetables instead of fried foods as a side dish.
6) Split restaurant entrees and share with a family member (restaurant portions are often several servings)
7) Cut back on eating out by one or more meals per week, and prepare more meals at home.

For more information visit:
http://www.choosemyplate.gov/food-groups/downloads/TenTips/DGTipSheet12BeaHealthyRoleModel.pdf
In Spanish: http://www.choosemyplate.gov/downloads/DGTipSheet12BeAHealthyRoleModel-sp.pdf
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/eat-right/eating-out.htm
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/index.htm

Nonalcoholic Steatohepatitis Clinical Research Network
(NASH CRN)

Cysteamine Bitartrate Delayed-Release for the Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in Children (CyNCh) Trial

Standard Operating Procedures

Part VI: MRI Procedure Manual

Confidential

26 March 2013

NASH CRN
CyNCh Trial
Standard Operating Procedures – Part VI:
MRI Procedure Manual

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1. Overview of CyNCh Trial

The **Cy**steamine Bitartrate Delayed-Release for the Treatment of **N**onalcoholic Fatty Liver Disease (NAFLD) in **Ch**ildren (CyNCh) Trial is a multicenter, randomized, double masked placebo-controlled trial designed to evaluate if treatment with delayed release (DR) cysteamine in children with NAFLD improves liver disease severity when compared to placebo. The **primary endpoint** is centrally scored histological improvement in NAFLD from baseline to the end of 52 weeks of treatment. Each subject will have one liver biopsy before treatment and one after treatment.

One of the **secondary endpoints** of the CyNCh Trial is change in MRI-determined hepatic fat fraction.

This **Standard Operating Procedure Manual** describes the procedures to be used for the two CyNCh Trial MRI examinations (one at baseline before randomization, and the other 52 weeks after the start of treatment) for measuring this secondary endpoint.

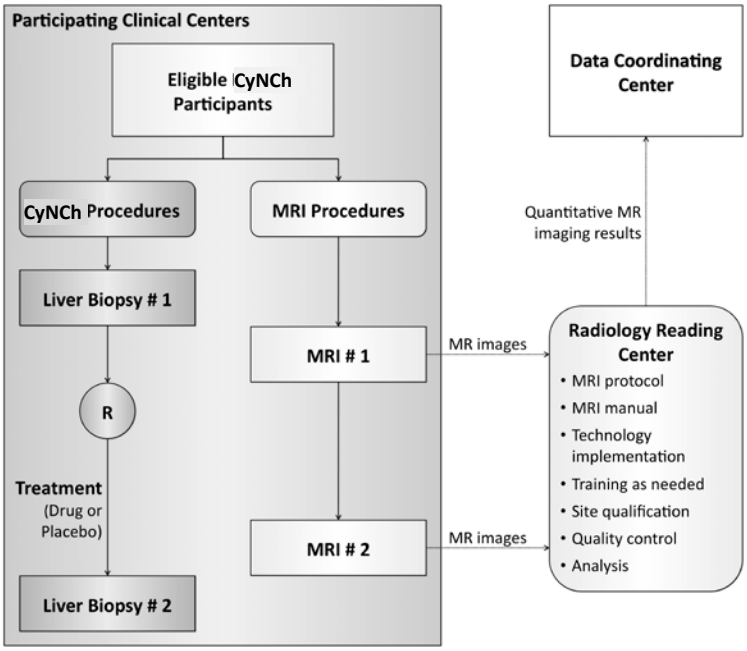
2. Study schema for MRI procedures in CyNCh Trial

The study schema is shown in **Figure 1**.

The first MRI examination will be performed: as close as possible to, and no more than 90 days from, the first liver biopsy.

The second MRI examination will be performed as contemporaneously as possible to, and no more than 6 weeks before and no more than 12 weeks after, the post-treatment biopsy at the 52-week visit. MRI examination scheduling is discussed further in **Section 9**.

Figure 1. Study Schema



Liver biopsies and MRI examinations will be performed at participating NASH CRN Centers. MR images will be sent to the CyNCh Radiology Reading Center (RRC) for central quality control and quantitative image analysis. The RRC will send quantitative MR imaging results to the NASH CRN Data Coordinating Center (DCC). Two MRI examinations will be performed. The first MRI will be performed before randomization (biopsy #1). The second MRI will be performed around the time (preferably before) of the end-of-treatment biopsy (biopsy # 2).

Liver biopsies and MRI examinations will be performed at participating NASH CRN Centers. The Center Radiologist will review the MR images qualitatively, will complete a **CyNCh MRI Radiologist Report CRF** (see **Appendix B**), and will inform a Center Hepatologist of any clinically significant findings. MR images on CD/DVD will be shipped to the CyNCh Radiology Reading Center (RRC; see **Section 4**) for central quality control and quantitative image analysis. The CyNCh RRC will send quantitative imaging results to the NASH CRN Data Coordinating Center (DCC).

3. Implementation of MRI examinations in CyNCh Trial

All Centers must obtain IRB approval from their own institution before performing MRI examinations as part of the CyNCh Trial.

MRI examinations are encouraged but not required for subjects enrolled in the CyNCh Trial. NASH CRN Centers may participate in the CyNCh Trial without offering MRI examinations, and research subjects may choose not to undergo MRI examinations and still enroll in the CyNCh Trial. As the MRI examinations are optional, subjects will be asked to sign a separate consent form for them, in addition to providing consent to participate in the CyNCh Trial.

Centers that elect to offer MRI examinations will undergo an MRI qualification process (see **Appendix D**, and **Section 18**); MRI will be phased in at qualifying Centers as soon as possible after those Centers have initiated the CyNCh Trial.

4. CyNCh Radiology Reading Center (RRC)

The CyNCh RRC will be run through the Liver Imaging Group, Department of Radiology, UC San Diego. The RRC will provide centralized quality control and quantitative MR image analysis, as well as other functions listed in **Figure 1**.

5. CyNCh RRC contact information

For any questions about the MRI procedures described in this manual, please contact one of the following RRC personnel:

FIRST CALL	SECOND CALL	THIRD CALL
Gavin Hamilton, PhD (619) 471-0511 office ghamilton@ucsd.edu	Michael Middleton, MD PhD (619) 471-0513 office (858) 750-0878 cell (619) 290-8250 pager msm@ucsd.edu	Claude Sirlin, MD (619) 471-0513 office (619) 709-3341 cell csirlin@ucsd.edu

6. Shipping MRI examinations to the RRC

As explained in **Section 16**, if CDs/DVDs are being shipped, one CD/DVD for each MRI examination performed should be **shipped to**:

Lisa Clark, MPH PhD
Laboratory Manager
CyNCh Radiology Reading Center (RRC)
MR3T Laboratory
408 Dickinson Street
San Diego, CA 92103-8226

phone: (619) 471-0513
fax: (619) 471-0503
email: liclark@ucsd.edu

CDs/DVDs may be mailed in weekly batches, or more often than that if so desired by Center personnel.

7. Purpose of MRI examination

The **primary purpose** of the MRI examinations in the CyNCh Trial is to quantify the hepatic **proton density fat fraction** (PDFF) non-invasively. PDFF is the proportion of mobile protons in liver tissue attributable to fat, and thus is a non-invasive MRI-based biomarker of liver triglyceride concentration. To quantify PDFF, the MRI examinations will utilize a non-contrast, single breath-hold, fast spoiled gradient-recalled echo (FSPGR) sequence that uses a low flip angle to reduce T1 bias, acquires multiple echoes after a single excitation to measure and correct for T2* relaxation, and uses spectral modeling to address fat-water and fat-fat signal interference effects.

The **secondary purpose** of the MRI examinations in this study is to collect and bank adiposity images of the entire abdomen and pelvis. Such images may be used to quantify abdominal (extrahepatic) adipose tissue compartment volumes in future ancillary studies.

8. MRI eligibility

Inclusion

- Enrolled in the CyNCh Trial
- CyNCh Registration completed, unless otherwise approved by the DCC
- Willing and able to complete MRI examination procedures

Exclusion

- Contraindication to MRI
- Extreme claustrophobia
- Pregnant or trying to become pregnant
- Weight or girth exceeds MRI scanner capabilities
- Any condition or circumstance that, in the opinion of the Center investigator, would interfere with completion of the MRI examination

9. MRI examination scheduling

Each subject will be scheduled locally at each Center by NASH CRN personnel for **TWO MRIs**:

MRI #1: Screening visit (Baseline MRI)

- To be scheduled before randomization
- To ensure that MRI examinations are done only on CyNCh-eligible subjects, we recommend that CyNCh eligibility with biopsy results be the trigger for scheduling the baseline MRI examination.
- The baseline MRI examination should be scheduled as contemporaneously as possible to, and no more than 90 days from, the pre-treatment biopsy.
- If possible, each Center will schedule their first two subjects at times when RRC personnel are available for telephone consultation.

Please schedule MRI #1 before randomization, and as close as possible to the pre-treatment biopsy.

Please schedule MRI #2 as close as possible to (preferably before) the end-of-treatment biopsy. Also, please schedule for as close as possible to the same time of day as MRI #1.

MRI #2: Post-treatment visit (Week-52 MRI)

- To be scheduled near the end of treatment.
- The post-treatment MRI should be scheduled as contemporaneously as possible to, and not more than 6 weeks before and not more than 12 weeks after, the post-treatment biopsy at the 52-week visit, and as close as possible to the **same time of day** as when the baseline MRI examination was performed.
- Ideally, the post-treatment MRI examination will be done before the post-treatment biopsy. The post-treatment MRI examination can be done after the post-treatment biopsy if it is not possible to schedule it before that biopsy.

10. Instructions to be given to subject during scheduling

At the time of scheduling, subjects should be informed that, if possible, they are to fast for four or more hours prior to their MRI examination, and that medications with sips of water will be allowed.

11. Subject and MRI examination identification

Each CyNCh research **subject** will be identified by a**:**

- NASH CRN Center Subject ID (*####*)
- NASH CRN Center Subject Code (*aaa*)

in the following format:

CYNCH_####_aaa

If this information is not available prior to enrolling subject, please contact the NASH CRN study coordinator before enrolling the subject.

Each CyNCh **MRI scan** will be identified in study paperwork and CD/DVD labeling (see also **Section 14**) in the following format:

CYNCH_####_aaa_ddmmmyy

where:

- ***####*** is the 4-digit NASH CRN Center Subject ID Number
- ***aaa*** is the 3-letter NASH CRN Center Subject Code
- ***ddmmmyy*** is the MRI date (day, month, year)

The NASH CRN Center IDs used in this study are listed in **Table 1** (right).

Note: You may enter the subject name coded as above in the MRI scanner, or you may enter subjects' real names in the MRI scanner if policy at your Center does not allow anonymized names to be entered into the scanner. If real names are entered in the scanner, please de-identify images afterwards, before CD/DVDs are burned and images are sent to the RRC.

Please ensure that no personal subject information (name, medical record number, accession number, DOB, etc.) is included in the electronic imaging data or on any submitted documentation, or is entered on the MRI scanner or scanner log (see Exception at left).

The NASH CRN Center ID code (*2-4 letters*) **that should be used on all CRFs should be for the Center from which the subject was recruited.**

TABLE 1. NASH CRN Center ID codes

BCM	Baylor College of Medicine, Texas Children's Hospital
CINC	Cincinnati Children's Hospital Medical Center
CU	Columbia University Medical Center
EU	Emory University
NWU	Northwestern University, Children's Memorial Hospital
IU	Indiana University
SLU	St. Louis University
UCSD	University of California, San Diego
UCSF	University of California, San Francisco
UW	University of Washington, Seattle Children's Hospital

12. CyNCh MRI Examination Log

A handwritten **CyNCh MRI Examination Log (Appendix F**) will be kept in a secure, locked location at each NASH CRN Center. It should **not** be taken out of the NASH CRN Center, and in particular should not be faxed or sent to the DCC or to the RRC, and should **not** be keyed into any online facility, since it will contain personal health information. The purpose of this log is to provide, for patient safety and reporting purposes, a definitive on-site record of who is having each scan.

The columns in the **CyNCh MRI Examination Log** are:

1. MRI examination number
2. NASH CRN Center Subject ID and Code
3. Subject name: last, first, middle initial
4. Date and time consent form signed
5. Subject date of birth
6. Subject gender
7. MRI examination date and start time
8. MRI examination completion code (0-2; see **Table 2**, to right)
9. Number of adverse events during MRI examination
10. Notes, including date CD/DVD sent to CyNCh MR Radiology Reading Center (if shipped), and any notes including the reason for any completion code < 2 in column #9

TABLE 2 MRI COMPLETION CODES (FIELD # 8)

0	MRI examination not started (0 images obtained)
1	MRI examination started (1 or more images obtained)
2	MRI examination completed

13. Coordinator responsibilities before each MRI examination

- **Review** the following basic information with subjects:
  1. Subjects to fast for four or more hours if possible before the MRI examination.
  2. Necessary medications are allowed with small amounts of water.
  3. Rehearse breathing instructions with subject. Subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and to reduce discomfort associated with breath-holding.
  4. Explain the necessity of remaining still during the MRI examination.

- **Confirm** the following information with subjects:
  1. Enrollment in CyNCh Trial
  2. Subject identity
  3. MRI consent has been signed (ask subject or coordinator)
  4. No contraindications to MRI, such as claustrophobia, pregnancy, weight exceeds scanner table limit, girth exceeds scanner bore diameter, and other conditions determined by Center investigators as potentially interfering with subject's ability to complete study
  5. Subject has emptied bladder prior to scanning
  6. Subject is wearing, or has changed into comfortable MRI-compatible clothing (no metal or metallic/shiny clothing)

- **MRI Safety Screening**

  Each subject should be screened for MRI safety using an institutional MRI screening form prior to each MRI examination. We recommend that subjects be screened in advance of each MRI examination if possible (e.g., at the time of obtaining MRI informed consent, or of MRI scheduling), but in all cases before they enter the MRI scanner room. Imaging personnel should review the screening form immediately prior to performing each MRI examination.

14. MRI Technologist responsibilities before each MRI examination

- **Confirm** the following **before placing subject into scanner**:
  1. MRI technologist will confirm verbally with the subject their name and date of birth
  2. MRI technologist will confirm verbally with the subject, or with the CyNCh Center Coordinator, that the **CyNCh MRI Consent Form** has been signed and dated by the subject
  3. To ensure that there are no MRI safety contraindications, the institutional MRI screening form should be reviewed, or if not yet completed it should be completed by the subject at that time and reviewed by the MRI technologist, before the subject is permitted to enter the MRI scanner room
  4. MRI-compatible clothing (no metal or metallic/shiny clothing)
  5. Bladder emptied
  6. Breathing instructions rehearsed and understood (subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and reduce discomfort associated with breath-holding)

- **Pre-MRI preparation:**
  1. Subjects to be positioned supine
  2. Ensure subject comfortable on scanner table
  3. For 3T MRIs, place dielectric pad over liver
  4. Place phased-array coil (over dielectric pad, for 3T scanners) centered over the liver; ensure good connection to scanner
  5. **A. If anonymized name entry for imaging studies is allowed at your institution:**

     The **last-name-field** in the MRI scanner as will be completed for each subject as:

     CYNCH_####_aaa_ddmmmyy

     where: **####** is the NASH CRN Center Subject ID,
     aaa is the NASH CRN Center Subject Code,
     and **_ddmmmyy_** is the date of the MRI.

     The **first-name field** in the MRI scanner will be left blank.

     The **medical-record-number field** in the MRI scanner will be left blank or completed with a series of 0's if an entry is required.

     The **date-of-birth field** in the MRI scanner will be left blank, or completed with 01-01-01 if an entry is required.

     B. If policy at your Center does <u>not</u> allow anonymized names to be entered into the scanner:

     Enter the subject's real name, and de-identify images afterwards, before CD/DVDs are burned and images are sent to the RRC.

- **MRI Safety Screening**

  Each subject should be screened for MRI safety using an institutional MRI screening form prior to each MRI examination. We recommend that subjects be screened in advance of each MRI examination if possible (e.g., at the time of obtaining MRI informed consent, or of MRI examination scheduling), but in all cases before they enter the MRI scanner room. Imaging personnel should review the screening form immediately prior to performing each MRI examination.

15. MRI scanning protocol

- Enter date and time that MRI examination was started into **CyNCh MRI Examination Log**

- All sequences will be acquired during **suspended respiration at end-inspiration**

- The following **sequences** will be run for all subjects:

  1. 3-plane localizer
  2. Coronal T2w SSFSE (or equivalent, all of abdomen and pelvis; repeat as necessary)
  3. Axial T2w SSFSE (or equivalent, all of abdomen and pelvis; repeat as necessary)
  4. 6-echo gradient-echo fat fraction 2D imaging – upper part of liver ("LQ High")
  5. 6-echo gradient-echo fat fraction 2D imaging – lower part of liver ("LQ Low")
  6. Adiposity 3D imaging – top to mid abdomen ("ADIP High")
  7. Adiposity 3D imaging –mid abdomen to femoral heads ("ADIP Low")

  [Each of sequences # 4-7 may be repeated up to a total of three times, but only if necessary to ensure adequate imaging coverage and quality. If adequate imaging coverage and quality are obtained, these sequences should not be repeated.

- For **6-echo gradient-echo fat fraction 2D imaging sequences** (#4 to #5), ensure that:

  1. Phased array coil is used
  2. Entire liver is imaged
  3. There is about a 4 cm overlap between acquisitions (i.e., between sequences #4 and #5)
  4. At least one slice for sequence #4 is obtained above the liver
  5. At least one slice for sequence #5 is obtained below the liver
  6. Correct parameters used (see **Tables 3** and **4**, below)
  7. Name the sequences "LQ High", "LQ Low"

- For **Adiposity sequences** (#6 to #7), ensure that:

  1. Body coil is used (do NOT need to remove phased array coil but **please make sure images are acquired with body coil**)
  2. Entire abdomen and pelvis are imaged
  3. There is about a 4 cm overlap between adiposity acquisitions (i.e., between sequences #6 and #7)
  4. At least one slice for sequence #6 is obtained above the liver
  5. At least one slice for sequence #7 is obtained at or below the level of the femoral heads
  6. Correct parameters used (see **Tables 3** and **4**, below)
  7. Name the sequences "ADIP High", "ADIP Low"
  8. All adiposity images are interpolated to 512 x 512 at time of acquisition

- For all sequences obtained after the localizer (#2 to #7), ensure that:

  1. Adequate field-of-view is used to avoid wrap-around artifact
  2. Sequences #1 to #3 are checked and repeated as needed if there is technical error
  3. Sequences # 4 to #7 are checked by the MR Technologist as they are done, and technical errors are corrected in any repeated sequences
  3. Review instructions with subject and repeat sequence if there is motion artifact
  4. All technical errors and image artifacts are resolved before proceeding to next sequence

Table 3. Imaging Parameters for MRI examinations at 1.5T

Sequence	Coil	Coverage	PSD	TR (msec)	TE (msec)	FA	Matrix	FOV	Phase FOV	ST (mm)	Gap (mm)	Sat
Coronal and Axial T2w SSFSE	Torso array	All of liver	2D SSFSE (GE), HASTE (Siemens), SSTSE (Phillips)	Min	Min	90°	256 x 192	Max	100%	10	0	No fat saturation
6-echo gradient-echo 2D	Torso array	Upper and lower parts of liver (2 sequences)	2D FSPGR (GE), FLASH (Siemens), T1 FFE (Phillips)	150	6 echoes: 2.3, 4.6, 6.9, 9.2, 11.5, 13.8 ms	10°	192 x 128 *or* 192 x 92	Max	60-100%	10	0	No fat or spatial saturation
Adiposity 3D	Body coil	Diaphragm to femoral heads in two equal acquisitions	3D FSPGR (GE), VIBE (Siemens), FFE (Phillips)	Min	Min	10°	256 x 192*	Max	60-100%	5-10	0	No fat or spatial saturation

* - Please interpolate all adiposity images **up to 512 x 512** at time of acquisition

Table 4. Imaging Parameters for MRI examinations at 3.0T

Sequence	Coil	Coverage	PSD	TR (msec)	TE (msec)	FA	Matrix	FOV	Phase FOV	ST (mm)	Gap (mm)	Sat
Coronal and Axial T2w SSFSE	Torso array	All of liver	2D SSFSE (GE), HASTE (Siemens), SSTSE (Phillips)	Min	Min	90°	256 x 192	Max	100%	10	0	No fat saturation
6-echo gradient-echo 2D	Torso array	Upper and lower parts of liver (2 sequences)	2D FSPGR (GE), FLASH (Siemens), T1 FFE (Phillips)	150	6 echoes: 1.15, 2.3, 3.45, 4.6, 5.75, 6.9 ms	10°	192 x 128 *or* 192 x 92	Max	60-100%	10	0	No fat or spatial saturation
Adiposity 3D	Body coil	Diaphragm to femoral heads in two equal acquisitions	3D FSPGR (GE), VIBE (Siemens), FFE (Phillips)	Min	Min	10°	256 x 192*	Max	60-100%	5-10	0	No fat or spatial saturation

* - Please interpolate all adiposity images **up to 512 x 512** at time of acquisition

16. Coordinator and MRI Technologist responsibilities after each MRI examination

- Center Coordinator to complete **MRI Data Transmittal CRF (**see **Appendix A**)
- Ensure that Center Radiologist completes **MRI Radiologist Report CRF** (see **Appendix B**), whether or not there are clinically significant incidental findings. If there <u>are</u> any clinically significant incidental findings, ensure that Center Radiologist notifies a Center Hepatologist.
- Center Coordinator to complete **MRI Adverse Event CRF** (see **Appendix C**), whether or not there are adverse events. If there <u>are</u> adverse events, the Center Coordinator should notify a Center Hepatologist.
- Please send **MRI Data Transmittal CRF** (see **Appendix A**), **MRI Radiologist Report CRF** (see **Appendix B**), and **MRI Adverse Event CRF** to Lisa Clark, MPH PhD, along with image CD/DVD (address below).
- **Burn** MRI examination to **three** CDs/DVDs. Label each CD/DVD **<u>ONLY</u>** as follows:

  CYNCH_####_aaa_ddmmmyy

  where: ***####*** is the 4-digit NASH CRN Center Subject ID Number
  aaa is the 3-letter NASH CRN Center Subject Code
  ddmmmyy is the date of the MRI (day, month, year)

- Ship CDs/DVDs to CyNCh Radiology Reading Center (RRC):

  Lisa Clark, MPH PhD
  Laboratory Manager
  CyNCh Radiology Reading Center (RRC)
  MR3T Laboratory
  408 Dickinson Street
  San Diego, CA 92103-8226

  phone: (619) 471-0513
  fax: (619) 471-0503
  email: liclark@ucsd.edu

  CDs/DVDs may be mailed in weekly batches, or more often than that if so desired by Center personnel.

- Ensure that all CyNCh MRI workflow procedures (see **Appendix E**) have been performed
- Ensure that **CyNCh MRI Examination Log** (see **Appendix F**) is complete, including that the "**study completion code**", number of adverse events, and any necessary notes into that log
- Store any CDs/DVDs that are not shipped to the RRC site at the Center in a secure location.

17. Center Radiologist responsibilities after each MRI examination

- Review MRI images
- Communicate any clinically relevant findings to a CyNCh Center Hepatologist
- Complete **MRI Radiologist Report CRF** (see **Appendix B**).

18. Qualification of NASH CRN CyNCh Centers

- The CyNCh RRC will qualify all Centers for participation in the CyNCh Trial.
- All Centers must obtain IRB approval from their own institution before performing MRI examinations as part of the CyNCh Trial.
- Each Center will complete a **CyNCh MRI Center Regulatory Qualification Form** and a **CyNCh MRI Center Technical Qualification Form** (see **Appendix D**).
- The CyNCh Radiology Reading Center (RRC) will confirm that, at each Center:
    1. Center **CyNCh MRI Examination Log** is initiated
    2. Scanner software successfully installed and operational, including 6-echo gradient-echo fat fraction 2D imaging, and 3D adiposity
    3. All Center personnel trained in use of all sequences
    4. The first subject may serve as the (first) volunteer. Scanning of the second and later subjects is contingent on acceptance of images from first subject (or of 1-2 volunteers) by the RRC.
    5. If volunteers are imaged, that data should be anonymized, backed up on three CDs/DVDs at site and sent (one CD/DVD) to CyNCh Radiology Reading Center (RRC), and the remainder of CDs/DVDs stored at Center in secure location
- Center qualification will continue after images received at CyNCh Radiology Reading Center (RRC) by confirming that:
    1. **CyNCh MRI Data Transmittal CRF** received and correlated with images received on CD/DVD
    2. Correct sequences and parameters verified for received images
    3. Received images analyzable
    4. Any problems communicated to Center, and repeat volunteer imaging requested
- Following successful Center qualification, the first two CyNCh Trial subjects at each Center will be imaged with RRC personnel on standby, if possible.

19. Appendices

Appendix A CyNCh MRI Data Transmittal Procedure
Appendix B CyNCh MRI Radiologist Report Procedure
Appendix C CyNCh MRI Adverse Event Procedure
Appendix D CyNCh MRI Center Qualification Procedure
Appendix E CyNCh MRI Workflow
Appendix F CyNCh MRI Examination Log

20. Case Report Forms

CyNCh MRI Data Transmittal CRF
CyNCh MRI Radiologist Report CRF
CyNCh MRI Adverse Event CRF

21. Center Qualification Questionnaires

CyNCh MRI Regulatory Questionnaire
CyNCh MRI Technical Questionnaire

APPENDIX A. CyNCh MRI DATA TRANSMITTAL PROCEDURE

In addition to completing the **CyNCh MRI Consent and Report Form** online for the DCC, the clinical coordinator at each Center will inform the **Radiology Reading Center** (RRC) of the numbers of MRI images in each series that were obtained, and other MRI examination data, by completing a **CyNCh MRI Data Transmittal CRF**, and will ship the images to the RRC on CD/DVD.

A. CyNCh MRI Data Transmittal CRF

A Radiology Reading Center (RRC) **CyNCh MRI Data Transmittal CRF** is to be completed for each MRI performed.

Items #1 (p1) **and #10** (p2)**:** The 2-4 letter code is for the **RECRUITING CENTER** (i.e., *CINC, CU, EU, NWU, IU, SLU, BCM, UCSD, UCSF, or UW)*

Section #13 consists of a list of the (minimum) 6 required series' for the CyNCh Trial:

1. Localizer – as per site preference
2. Coronal T2-weighted SSFSE (all of abdomen and pelvis) – breath-hold
   - repeat if there is motion artifact
   - ensure that coverage goes down to bottom of pelvis
3. Axial T2-weighted SSFSE (also all of abdomen and pelvis) – breath-hold
   - repeat if there is motion artifact
   - ensure that coverage goes down to bottom of pelvis
4. Axial 6-echo gradient-echo (fat quantification) 2D – whole liver if possible, or superior and inferior liver separately if whole liver coverage in one sequence is not possible:
   - repeat each acquired sequence up to a total of 3 times, but only if needed to ensure that all of liver is covered and that image quality is not unacceptable. If all of the liver is covered and image quality is acceptable, do not repeat.
   - If the full liver not covered in a single breath-hold, do an axial 6-echo gradient-echo (fat quantification) 2D sequence to cover the inferior liver. If more than one sequence is acquired to achieve full liver coverage, overlap between sequences should be about 4 cm.
5. (Axial) adiposity 3D – superior to mid abdomen
   - repeat each acquired sequence up to a total of 3 times, but only if needed to obtain coverage down to mid-abdomen and to ensure that image quality is not unacceptable. If coverage is obtained down to mid-abdomen and image quality is acceptable, do not repeat.
6. (Axial) adiposity 3D – mid abdomen to level of mid femoral heads
   - repeat each acquired sequence up to a total of 3 times, but only if needed to obtain coverage down to the mid femoral heads and to ensure that image quality is not unacceptable. If coverage is obtained down to the mid femoral heads and image quality is acceptable, do not repeat. Overlap of the upper and lower adiposity sequences should be about 4 cm.

For each series, please enter: a) series number
b) number of images in that series

If a series is repeated, please enter the number of the series that contains the best images, or the one that was complete (if one or more was acquired that was incomplete).

Notes:
1. For **GE scanners**, additional series' may be generated by your scanner for series # 4 (and #5), usually with series numbers in the 9000's. Do **not** list them on the Data Transmittal CRF, but please do send them to the RRC.
2. Please send all acquired images to the RRC.
3. For series' # 2 and #3, if repeated, please list the series number, and number of images, for the series' that have the best quality images

B. Create CDs/DVDs

1. Burn three copies of the study should be burned to CDs/DVDs
2. Label each CDs/DVD in the following format:

CyNCh_####_aaa_ddmmmyy

where:	*####*	is the 4-digit NASH CRN Center Subject ID number
	aaa	is the 3-letter NASH CRN Subject Code
	ddmmmyy	is the MRI date (month, day, year)

C. Ship one CD/DVD to CyNCh Radiology Reading Center (RRC)

1. Place one of the three copies of the study on CD/DVD in a cardboard shipping box (e.g., DHL, FedEx, etc.).
2. Ship by two-day delivery service **with ability to track the shipment** to:

Lisa Clark, MPH PhD
Laboratory Manager
CyNCh Radiology Reading Center
MR3T Laboratory
408 Dickinson Street
San Diego, CA 92103-8226

phone: (619) 471-0513
fax: (619) 471-0503
Email: liclark@ucsd.edu

Shipments of CDs/DVDs may be batched and sent weekly, or more often, as per the preference of the Clinical Center.

APPENDIX B: CyNCh MRI RADIOLOGIST REPORT PROCEDURE

After reviewing the images, the Center Radiologist will complete an **MRI Radiologist Report CRF** for each MRI that is performed.

If there are **no significant abnormal findings**, one box may be checked indicating that, and the form signed and dated.

If there **<u>are</u> significant abnormal findings:**

a) one box may be checked indicating that, the findings described, and the form signed and dated

b) That information is to be provided to the Center Hepatologist for possible clinical follow-up, as needed

Please send a copy of that CRF to the CyNCh Radiology Reading Center (RRC), along with the CD/DVD containing the study images.

APPENDIX C: CyNCh MRI ADVERSE EVENT PROCEDURE

For each MRI that is performed, the study coordinator will complete an **MRI Adverse Event CRF.**

If there was **no adverse event**, one box may be checked indicating that, and the form signed and dated.

If there **was (one or more) adverse event(s):**

a) One box may be checked indicating that (one CRF per adverse event), and the findings described.

b) Each event should be characterized using the standard criteria, listed on that CRF.

c) That CRF should be signed and dated

d) A copy of that CRF should be provided to a Center Hepatologist for possible clinical follow-up, as needed.

Please send a copy of that CRF to the CyNCh Radiology Reading Center (RRC), along with the CD/DVD containing the study images.

APPENDIX D. CyNCh MRI CENTER QUALIFICATION PROCEDURE

A **CyNCh MRI Regulatory Qualification Form** and a **CyNCh MRI Technical Qualification Form** will be completed by each Center before any study subjects are scanned. They will contain the following information.

A. Personnel

The following information:

Name	Office phone number	Email address
Academic title	Cell phone number	
Actual address	Fax number	

CITI IRB certification completion date (please email to Lisa Clark MPH PhD at RRC, at liclark@ucsd.edu)

will be collected for the:

Center Radiologist
Center Hepatologist #1 (and Center Hepatologist #2 if there is one)
Center Coordinator - primary contact with the CyNCh Radiology Reading Center (RRC)

B. Center IRB approval status

Confirmation that the following have been sent or faxed to the CyNCh Radiology Reading Center (RRC):

a) Center IRB-approved **MRI Consent Form**
b) Center IRB-approved **Research Plan** (at our institution, this is a 30-question form where we tell our IRB what we will be doing)
c) Center IRB **Approval Letter**

C. MRI scanner, hardware, software

The following information will be provided to the CyNCh Radiology Reading Center (RRC):

Scanner manufacturer and model, field strength, software version, physical location (address)
Confirmation that the 6-echo gradient-echo fat quantification 2D sequence successfully installed
Confirmation that the ADIPOSITY sequence successfully installed
Confirmation that all MRI technologists been trained in the use of all hardware and software

D. Volunteer (or first subject) imaging

The first subject may serve as the (first) volunteer. Scanning of the second and later subjects is contingent on acceptance of images from the first subject (or the volunteers) by the RRC. Confirmation will be provided to the Radiology Reading Center (RRC) that, for the first subject, or for 1-2 volunteers:

All workflow procedures listed in **Appendix E** to this SOP have been followed
The study dates of each of the volunteers (or the first subject)
Confirmation that the correct parameters were used for all sequences
Confirmation that all images obtained are de-identified
Confirmation that 3 CDs/DVDs burned for each volunteer (or the first subject)
Confirmation that all DCC and RRC CRFs have been completed, and that the images have been successfully transferred to UCSD

APPENDIX E. CyNCh MRI WORKFLOW

This document describes the overall workflow for a typical CyNCh MRI examination.

A. Before MRI examination

The clinical coordinator should review the following information with the subject:

1) Subjects should fasting for four or more hours if possible before the MRI examination.
2) Necessary medications are allowed with small amounts of water.

B. On day of MRI examination, before MRI is performed

The MRI technologist should confirm with the subject the following information before the MRI is performed:

1) Subject identity
2) MRI consent has been signed (ask subject or coordinator)
3) No MRI contraindications
4) Bladder emptied prior to scanning
5) MRI-compatible clothing (no metal or metallic/shiny clothing)
6) Breathing instructions rehearsed and understood (subjects will be asked to hold breath in end-inspiration to maximize breath-hold capacity and reduce discomfort associated with breath-holding).

C. When subject on MRI table, before scan started

The MRI technologist should confirm that:

1) Subject to be positioned supine
2) Ensure subject comfortable on scanner table
3) For 3T MRIs, place dielectric pad over liver
4) Place phased-array coil (over dielectric pad, for 3T scanners) centered over the liver; ensure good connection to scanner

D. After MRI examination

1) Center Radiologist to review images and to complete **CyNCh MRI Radiologist Report CRF** to indicate that that review has been done
2) Center Radiologist to notify CyNCh Center Hepatologist(s) if there were significant findings on MRI examination
3) Clinical coordinator to complete **CyNCh MRI Adverse Event CRF** to indicate whether or not there were any adverse events
4) Clinical coordinator to burn three copies of study to CD/DVD - one to send to RRC, and two to save onsite in a secure location
5) Clinical coordinator to enter series numbers and number of images in each series into the **CyNCh MRI Data Transmittal CRF**
7) Ship CD/DVD to:

Lisa Clark, MPH PhD
Laboratory Manager
CyNCh Radiology Reading Center (RRC)
MR3T Laboratory, 408 Dickinson Street, San Diego, CA 92103-8226
Phone: (619) 471-0513
Fax: (619) 471-0503
Email: liclark@ucsd.edu

8) Clinical coordinator to complete **MRI Examination Log** (to be kept on site at center, not to be transmitted or sent to the RRC or to the NASH CRN)

CyNCh MRI Examination Log

NASH CRN Center ID (*2-4 letters*): _____ (of recruiting center: i.e.: CINC, CU, EU, NWU, IU, SLU, BCM, UCSD, UCSF, UW**)**

Center IRB#: _____ **Expiration date of Center IRB-approved Consent Forms: _____**

Completion codes (CC):

0 = MR examination not started (0 images obtained)
1 = MRI started but not completed (1 or more images obtained; please state reason in notes)
2 = MRI completed

1. Keep in secure location at NASH CRN Center
2. Do **NOT** send to NASH CRN
3. Do NOT send to CyNCh Radiology Reading Center

MRI examination #	NASH CRN Center Subject ID and Code (#### *aaa*)	Name (Last, First, MI)	Date and Time Consent Signed	Date of Birth	M/F	MRI examination			Notes (including reason for completion codes < 2)
						Date and Time	CC	# AEs	
									Date CD/DVD sent: _____ Notes:
									Date CD/DVD sent: _____ Notes:
									Date CD/DVD sent: _____ Notes:

CyNCh MRI DATA TRANSMITTAL CRF

Instructions:

- Please complete this **MRI Data Transmittal CRF** for each MRI examination performed
- Burn MRI examination to **three** CDs/DVDs (please include all acquired images)
- **Shipping:**
  - Place one of the CDs/DVDs in a cardboard shipping box (e.g., DHL, FedEx)
  - Fax a copy of this **MRI Data Transmittal CRF** to the CyNCh Radiology Reading Center (RRC) to:
    Attention: Lisa Clark, MPH PhD
    Fax number: (619) 471-0503
  - Arrange for two day delivery service **with ability to track the shipment** to:

Lisa Clark, MPH PhD
Laboratory Manager
CyNCh Radiology Reading Center
MR3T Laboratory
408 Dickinson Street
San Diego, CA 92103-8226
phone: (619) 471-0513
fax: (619) 471-0503
email: liclark@ucsd.edu

A. Center/Subject ID, and shipping and MRI examination status

1. **NASH CRN Center ID** (2-*4 letters*)**:** ___ ___ ___ ___ *(**recruiting** center: i.e.: BCM, CINC, CU, EU, NWU, IU, SLU, UCSD, UCSF, or UW)*

2. **NASH CRN Subject ID** *(####)***:** ___ ___ ___ ___

3. **NASH CRN Subject Code** *(aaa)***:** ___ ___ ___

4. Was MRI examination started (subject placed in MRI scanner)? (*If no fill in reason and skip to **#14***)
☐**Yes** ☐**No** (if **No**, reason? _____

MRI examination completion status:
☐No images obtained
☐Started but not completed *(at least 1 image obtained)*
☐Completed (all required images obtained)

5. **Date of MRI examination:** ___ ___ - ___ ___ ___ - ___ ___
dd *mmm* *yy*

6. **Start time of MRI examination:** ___ ___ : ___ ___
(24h)hh *mm*

7. **Shipping/image transmittal service** *(check all that apply)***:** ☐DHL ☐FedEx ☐UPS ☐USPS
☐Other form shipping: _____

8. **Shipping Tracking Number** *(if applicable)***:** _____

9. **Comments or protocol deviations:** _____
_____
_____
_____
_____

B. MRI shipment information (*please record information about **one subject only** on each CD/DVD.*)

10. **NASH CRN Center ID** (2-*4 letters*)**:** ___ ___ ___ ___ *(of **recruiting** center: i.e.: BCM, CINC, CU, EU, NWU, IU, SLU, UCSD, UCSF, or UW)*

11. **NASH CRN Subject ID** *(####)***:** ___ ___ ___ ___

12. **NASH CRN Subject Code** *(aaa)***:** ___ ___ ___

13. **REQUIRED MRI sequences**

		Series #	# Images	
13.1.	**Localizer**	_____	_____	
13.2	**Coronal T2-weighted SSFSE** (or equivalent)	_____	_____	*(best images)*
13.3	**Axial T2-weighted SSFSE** (or equivalent)	_____	_____	*(best images)*
	(diaphragm to bottom pelvis)	_____	_____	
13.4.	**Axial 6-echo grad-echo fat quant - superior liver**	_____	_____	*(can be whole liver)*
13.5.	**Axial 6-echo grad-echo fat quant - inferior liver**	_____	_____	*(if needed)*
13.6.	**Adiposity 3D –superior to mid abdomen** *(diaphragm to bottom pelvis)*	_____	_____	
13.7	**Adiposity 3D –mid abdomen to mid femoral heads** *(diaphragm to bottom pelvis)*	_____	_____	

C. Administrative

14. **Study Coordinator name:** _____

signature/date/time: _____

CyNCh MRI RADIOLOGIST REPORT CRF

Purpose:	To document whether there are, or are not, clinically significant incidental findings
When:	At time incidental findings are noted
To be completed by:	Clinical Coordinator
To be signed by:	Center Radiologist

A. Center/Subject/Examination ID

1. **NASH CRN Center ID** (2-*4 letters*)**:** ___ ___ ___ ___ *(of recruiting center: i.e.: BCM, CINC, CU, EU, NWU, IU, SLU, UCSD, UCSF, or UW)*

2. **NASH CRN Subject ID** *(####)***:** ___ ___ ___ ___

3. **NASH CRN Subject Code** *(aaa)***:** ___ ___ ___

4. **MRI examination date:** ___ ___-- ___ ___ ___--___ ___
dd mmm yy

5. **MRI examination start time:** ___ ___ : ___ ___
(24hr)hh mm

B. Description of incidental findings

6. Were there clinically significant incidental findings on the MRI examination?
☐Yes ☐No
(If **Yes** please comment below, and note which Hepatologist was contacted, and when contacted)

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

☐ Center Hepatologist contacted about these findings:

Name of Hepatologist: _____
Date contacted: _____

C. Administrative

7. **Center Radiologist name:** _____

signature/date/time: _____

CyNCh MRI ADVERSE EVENT CRF

Purpose:	To document adverse events
When:	At time of adverse event
To be completed by:	Clinical coordinator

A. Center/Subject/Examination ID

1. **NASH CRN Center ID** (2-*4 letters*)**:** ___ ___ ___ ___ *(of **recruiting** center: i.e.: BCM, CINC, CU, EU, NWU, IU, SLU, UCSD, UCSF, or UW)*

2. **NASH CRN Subject ID** *(####)***:** ___ ___ ___ ___

3. **NASH CRN Subject Code** *(aaa)***:** ___ ___ ___

4. **MRI examination date:** ___ ___-- ___ ___ ___--___ ___
dd mmm yy

5. **MRI examination start time:** ___ ___ : ___ ___
(24hr)hh mm

B. Description of adverse event

6. Were there any adverse events noted during the visit by MRI examination personnel? ☐**Yes** ☐**No**

If YES:

6a. Time of adverse event: ___ ___ : ___ ___ (24 hour time)

6b. Describe nature of adverse event *(onset, description, duration, resolution)*:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

6c. Did adverse event result in hospitalization? ☐Yes ☐No

6d. Severity? ☐Mild ☐Moderate ☐Severe

6e. Unexpected Adverse Event (UAE)? ☐Yes ☐No

6f. Severe Adverse Event (SAE)? ☐Yes ☐No

6g. Relation to Study Procedures? ☐Not related ☐Probably related ☐Possibly related ☐Definitely related

6h. Was a Center Hepatologist notified? ☐Yes ☐No (if **YES**, date? _____)
(name: _____)

C. Administrative

7. **Clinical coordinator name:** _____

signature/date/time: _____

CyNCh MRI CENTER REGULATORY QUALIFICATION QUESTIONNAIRE

1. Center Radiologist

[Please list below the contact information for the Center Radiologist; Check box to indicate CITI IRB Certification.]

Name: _____
Academic title: _____
Actual address: _____
_____
Email address: _____
Office phone number: _____
Cell phone number: _____ Date IRB CITI certification: _____
Fax number: _____ ☐ pdf copy emailed to Lisa Clark MPH PhD (liclark@ucsd.edu)

2. Center Hepatologist #1

[Please list below the contact information for the Center Hepatologist #1; Check box to indicate CITI IRB Certification.]

Name: _____
Academic title: _____
Email address: _____
Office phone number: _____
Cell phone number: _____ Date IRB CITI certification: _____
Fax number: _____ ☐ pdf copy emailed to Lisa Clark MPH PhD (liclark@ucsd.edu)

3. Center Hepatologist #2

[Please list below the contact information for the Center Hepatologist #2; Check box to indicate CITI IRB Certification.]

Name: _____
Academic title: _____
Email address: _____
Office phone number: _____
Cell phone number: _____ Date IRB CITI certification: _____
Fax number: _____ ☐ pdf copy emailed to Lisa Clark MPH PhD (liclark@ucsd.edu)

4. Center Coordinator

[Please list below the contact information for the Center Coordinator; Check box to indicate CITI IRB Certification.]

Name: _____
Email address: _____
Office phone number: _____
Cell phone number: _____ Date IRB CITI certification: _____
Fax number: _____ ☐ pdf copy emailed to Lisa Clark MPH PhD (liclark@ucsd.edu)

5. Center IRB Approval Status

Date of Center IRB approval: _____
Date IRB approval letter, consent, and research plan sent to CyNCh Radiology Reading Center (RRC): _____

Form completed by: _____ Date and time: _____

CyNCh MRI CENTER TECHNICAL QUALIFICATION QUESTIONNAIRE

1. MRI Scanner, Hardware, Software

Scanner Manufacturer and Model: _____
Scanner Field Strength: ☐1.5T ☐3.0T
Scanner Software version: _____

Scanner Location (address): _____

Has the StarMAP (or equivalent 6-echo gradient-echo) fat fraction sequence been successfully installed? ☐ date: _____

Has the ADIPOSITY sequence been successfully installed? ☐ date: _____

Have all MRI Technologists been trained in the use of all of the above hardware and software to the satisfaction of the Center Radiologist? ☐ date: _____

2. Volunteer Imaging (optional)

The first subject may serve as the (first) volunteer. Scanning of the second and later subjects is contingent on acceptance of images from first subject (or the volunteers) by the RRC.

First volunteer:

Study date: _____
Study start time: _____
Study name: _____ *(as registered at MRI scanner)*

Correct parameters used for all sequences?
☐Yes ☐No *(list deviations here):*_____

All study images anonymized?
☐Yes ☐No *(reason):* _____

All study images burned to 3 (three) CDs/DVDs?
☐Yes ☐No *(reason):* _____
[Please send #1 copy to CyNCh Radiology Reading Center (RRC); keep #2 and #3 copies at site]

Date that #1 copy of image CD/DVD sent to *CyNCh Radiology Reading Center (RRC)*: _____

Date ***MRI Data Transmittal CRF, MRI Radiologist Report CRF, and MRI Adverse Event CRF*** *faxed to: Lisa Clark MPH PhD (619-471-0503) at UCSD:* _____

Second volunteer:

Study date: _____
Study start time: _____
Study name: _____ *(as registered at MRI scanner)*

Correct parameters used for all sequences?
☐Yes ☐No *(list deviations here):*_____

All study images anonymized?
☐Yes ☐No *(reason):* _____

All study images burned to 3 (three) CDs/DVDs?
☐Yes ☐No *(reason):* _____
[Please send #1 copy to CyNCh Radiology Reading Center (RRC); keep #2 and #3 copies at site]

Date that #1 copy of image CD/DVD sent to *CyNCh Radiology Reading Center (RRC)*: _____

Date ***MRI Data Transmittal CRF, MRI Radiologist Report CRF, and MRI Adverse Event CRF*** *faxed to: Lisa Clark MPH PhD (619-471-0503) at UCSD:* _____

Form completed by: _____ Date and time: _____