Childhood Liver Disease Research and Education Network (ChiLDREN)

A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL OF CORTICOSTEROID THERAPY FOLLOWING PORTOENTEROSTOMY IN INFANTS WITH BILIARY ATRESIA

Manual of Operations (MOO)

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CHAPTER 1. OVERVIEW

1.1 Summary of Study

The overall hypothesis is that therapy with corticosteroids following portoenterostomy will improve bile drainage and long-term outcome in infants with biliary atresia. This hypothesis will be tested by a multi-center prospective, randomized, double-blinded, placebo-controlled trial. Subjects will be recruited from patients enrolled in the Childhood Liver Disease Research and Education Network (ChiLDREN) prospective observational database (PROBE) study, who undergo portoenterostomy for biliary atresia. The Principal Investigator (PI) or Clinical Research Coordinator (CRC) will approach the subject's parent(s) or legal guardian(s) and discuss the study design, benefits and possible risks with the family.

After Institutional Review Board (IRB)-approved written consent is obtained from the subject's parent(s) or legal guardian(s), the CRC will:

- Complete the Eligibility Form
- Randomize the subject to 13 weeks of treatment with placebo or corticosteroids. (The research team will be blinded to the treatment. The randomization scheme will be prepared by the University of Michigan (UM) Data Coordinating Center (DCC) and implemented by the research pharmacist.)
- Collect clinical and biochemical data at 2 weeks after portoenterostomy, at 1, 2, 3, and 6 months after portoenterostomy, and at 12, 18, and 24 months of age.

All subjects will receive standard clinical care that is routinely used for all infants with biliary atresia, which will include nutritional support and medications unrelated to this trial. This routine clinical care will not be modified due to participation in this study. One important feature of this clinical trial is that subjects will receive standard clinical care at ChiLDREN study sites, in addition to the care related to enrollment in the trial.

The trial will specifically require:

1) Randomization to receive either corticosteroids or placebo.
2) Treatment with ranitidine during the duration of study drug/placebo
3) Outpatient visit at 2 weeks after portoenterostomy
4) Serum concentration of electrolytes, glucose, bile acids, and Proteins Induced by Vitamin K Antagonism or Absence (PIVKA)-II.
5) Developmental assessment
6) Health-Related Quality of Life (HRQOL) inventory
7) Evaluation of serum antibody titers to vaccines.
8) Ophthalmology exam / cataract screening.
9) Assessment of vitamin levels.

All other outpatient visits and laboratory studies are routinely performed as part of standard clinical care of infants with biliary atresia.

CHAPTER 2. SCREENING AND RECRUITMENT

2.1 Population

The total number of subjects to be entered in the study at all study sites will be 140.

2.2 Screening/Recruitment Plan

Subjects will be recruited from patients evaluated at, referred to, and followed at the Childhood Liver Disease Research and Education Network (ChiLDREN) study sites, which have been consented and enrolled into the ChiLDREN prospective database study (PROBE) and found to have biliary atresia. The Principal Investigator (PI) or Clinical Research Coordinator (CRC) will recruit the subject's parent(s) or legal guardian(s) during clinic visits, or during an inpatient admission to the hospital when exploratory laparotomy and portoenterostomy are being planned for diagnosis and treatment of biliary atresia. If the subject's parent(s) or legal guardian(s) are not approached about the clinical trial before surgery, recruitment may also occur within 72 hours of the portoenterostomy. The investigator will discuss the study design, benefits and possible risks with the family. Printed information about the study and the informed consent form will be given to the family; questions about the study will be answered.

The Institutional Review Board (IRB)-approved consent will include:

- Purpose of the trial.
- Research procedures used in the trial.
- Responsible parties and investigators.
- Potential benefits.
- Risks of participation.
- Right to refuse to be in the study.
- Right to withdraw from the study under no penalty.
- Contact numbers and information about the responsibility for injury and payment for medical care.

2.3 Eligibility/Exclusion Criteria

All infants enrolled in the ChiLDREN prospective database study (PROBE) who undergo portoenterostomy or the gall bladder Kasai operation (portocholecystostomy) for biliary atresia will be eligible for the trial.

Eligibility: fulfillment of the inclusion/exclusion criteria. This data must be collected at recruitment. The CRCs will need to enter this data into the ChiLDREN website and complete the eligibility Case Report Form (CRF) S11.

2.3.1 Inclusion Criteria

- Portoenterostomy or gall bladder Kasai operation for biliary atresia within the previous 72 hours.
- Post-conception age ≥36 weeks.
- Weight at enrollment ≥2000 gm.
- Written informed consent to participate in the study obtained prior to or within 72 hours of completion of portoenterostomy. (Note: Families of potential subjects may be approached prior to the portoenterostomy.)

2.3.2 Exclusion Criteria

- Known immunodeficiency.
- Diabetes mellitus (glucose ≥200 mg/dL).
- Presence of significant systemic hypertension for age (persistent systolic blood pressure ≥112 mmHg).
- A serum indirect (unconjugated) bilirubin ≥5 mg/dL for infants under 4 weeks of age or ≥7 mg/dL for infants between 4 and 8 weeks of age.
- Known sensitivity to corticosteroids.
- Documented bacteremia or other tissue infection, which is felt to be clinically relevant.
- Known congenital infection or disease with herpes simplex virus, toxoplasmosis, or cytomegalovirus inclusion disease of the liver.
- Infants whose mother is known to have human immunodeficiency virus infection.
- Infants whose mother is known to be HBsAg or hepatitis C virus positive.
- Infants with other severe concurrent illnesses such as neurological, cardiovascular, pulmonary, metabolic, endocrine, and renal disorders that would interfere with the conduct and results of the study.
- Any other clinical condition that is a contraindication to the use of corticosteroid (e.g., bowel perforation).
- Infants who have received the live attenuated rotavirus vaccine (e.g. Rotateq) within 5 days prior to proposed administration of study drug.
  - Infants who have received the live attenuated rotavirus vaccine (e.g. Rotateq) within 5 days prior to proposed administration of study drug are excluded from the study. Infants who have received the vaccine prior to this interval should not receive their first dose of steroids until a total of 5 days post vaccination has elapsed.

In the unlikely event that the diagnosis of biliary atresia is established during exploratory laparotomy, but the surgeon did not perform a portoenterostomy (as may occur in cases of advanced cirrhosis), the patient will not be eligible for this study.

2.4 Exceptions to the Inclusion/Exclusion Criteria

Whenever the answer to an inclusion criterion is no or to an exclusion criterion is yes (even if the condition for the exclusion is fulfilled), an exception/exemption will be required.

When a PI is aware that a request for exception/exemption will be necessary, they can email the Data Coordinating Center (DCC) to have the Exemption Committee review the request prior to obtaining informed consent from the subject. The email should include a sequence number (Exx) for case identification, the exclusion criterion violated and the reason that an exemption is being requested. If approved and the subject is recruited, the Exemption Form would be completed at the time of consent and the DCC will indicate on it the approval of the request. (In order to enter data in the Exemption Request, Form 15, go to the Screening or Baseline section of the subject's CRF on the website.)

The Steering Committee (SC) requests that the DCC email the Exemption Committee with the results of the exemption vote. Pat Robuck from the National Institutes of Health (NIH) requests to be cc'd on these emails.

NOTE: If a subject has been consented and then a question about eligibility arises, please use Form 15. If ineligible, the research subject ID cannot be reused.

2.4.1 Details about Certain Eligibility Criteria

- **Blood pressure**: One of the START ineligibility criteria is significant hypertension, but there is no place provided to record the blood pressure. The blood pressure can be taken any time during the preceding 24 hours and therefore should be available in the hospital record. When this is not possible, the CRC may write the actual blood pressure on Form S11 next to the criterion and note that there is no other source document.

- **Criteria for bilirubin at the time of recruitment/eligibility:** A subject is eligible if at the time of recruitment the known bilirubin is in the eligible range. This blood draw may be from prior to the day of consent. The result of a blood draw that is known after consent does not affect eligibility.

- **Request for a protocol exemption:** If the subject does not meet eligibility criteria, the study site may submit a protocol exemption (form 15). This data is entered into the ChiLDREN website and is forwarded to the Exemption Committee. A response is forward to the study site within 2 days.

2.5 Screening/Enrollment Logs

The Screening/Enrollment Logs form can be either printed off of the ChiLDREN website or developed independently by study-sites to capture the essential information. In either circumstance, it should be kept up to date throughout the study.

- **Screening Form:** An essential document that records all individuals who entered pre-screening or screening and details the reasons why an individual was not enrolled. The screening log demonstrates the lack of bias in the selection of subjects and the investigator's attempt to enroll a representative sample of subjects. This log should be completed separately for each study.

- **Enrollment Log/Master Participant Log:** An essential document that records the enrollment of subjects. The Enrollment Log contains the study subject name or initials, study ID # and informed consent date. This log should be kept in a secured location with procedures in place regarding who has access to remove and under what conditions. With today's computer systems, this log may be an extension of an automated screening log or may be generated by the computer.

CHAPTER 3. INFORMED CONSENT

3.1 Informed Consent Document

The Data Coordinating Center (DCC) will provide a protocol-specific informed consent template for all the Childhood Liver Disease Research and Education Network (ChiLDREN) study sites. Each ChiLDREN study site will customize the template and receive approval from their study site's human subject protection committee.

The written informed consent should be brief and written in plain language so that a subject's parent(s) or legal guardian(s) who has not graduated from high school can understand the contents. An investigator, subject or subject's parent(s) or legal guardian(s) and witness should each sign and date the informed consent documents. The subject's parent(s) or legal guardian(s) should receive a copy of the signed and dated informed consent form. The study site must maintain a signed copy of the informed consent document for each subject in the study. Good Clinical Practice (GCP) guidelines require that source documents should indicate that the informed consent form was signed, along with the date of signing. No collection of data related to the study or to procedures will be done prior to completion of the informed consenting process.

3.2 Obtaining Informed Consent

For the START Trial, informed consent must be obtained within 72 hours from when the portoenterostomy was performed. Families of potential subjects may be approached prior to the portoenterostomy. Written informed consent will be obtained either after a decision is made by the attending physician at the ChiLDREN study site that the infant will undergo an exploratory laparotomy with possible portoenterostomy, or within 72 hours after portoenterostomy.

The study will be discussed in detail by the physician and Clinical Research Coordinator (CRC); and the informed consent reviewed.

The informed consent will include:

- Study purpose.
- Description of procedures.
- Risks and benefits.
- Alternative treatments.
- Costs.
- Compensation.
- Issues of confidentiality.

As part of the informed consent, the subject's parent(s) or legal guardian(s) will be informed of potential side effects of corticosteroids, as well as of potential adverse consequences of the sudden discontinuation of high doses of corticosteroids (after use for more than 2 weeks). Signed and dated informed consents will be obtained from the subject's parent(s) or legal guardian(s). The consent should be signed and dated by the investigator or designee (designee must be documented on the delegation log). Assent will not be sought from study subjects because they will be infants at entry into this study.

Failure to give informed consent renders the subject ineligible for the study. No research testing /exams or study medication will occur before informed consent has been obtained.

3.3 Re-Consent

If there is a change in any of the study procedures that may affect the subject, the informed consent document must be revised and again approved by the Institutional Review Board (IRB). Any subjects enrolled in the study prior to such changes may be required to sign an amended consent form, dependent on local IRB requirements.

3.4 Health Insurance Portability & Accountability Act (HIPAA) Compliance

At most study sites, a HIPAA form is presented to a potential subject for signature, in addition to the informed consent form, unless the necessary assurances are incorporated into the informed consent form. The HIPAA form describes subject and data confidentiality associated with the study.

3.5 Non-English-Speaking Subjects

Many IRB's mandate whether a translated consent document is needed to obtain consent from non-English speaking subjects or whether a translator can be used to obtain consent. Each study site must conform to their local requirements. With respect to completing Case Report Forms (CRFs), each study site should attempt to do their best to avoid errors as a result of translation.

3.5.1 Other issues related to translators

- A Human Protection certificate is not needed for the translator because the translator is only translating what the health care professional is stating; they do not provide patient care or collect data.
- Translation of any instructions is the responsibility of the study site and should be handled in the same manner as for non-research subjects.

- All expenses and budget issues related to using translators are study site-specific and should be discussed with the Principal Investigator (PI).

  NOTE: Translator issues are study-site specific; they are the responsibility of the study site / PI.

CHAPTER 4. STUDY VISIT DETAILS

4.1 Visit Descriptions

Following portoenterostomy and discharge from the hospital, subjects will be evaluated in the outpatient clinic **2 weeks after portoenterostomy**, at **1, 2, 3, and 6 months after portoenterostomy**, and then at **12, 18, and 24 months of age.** Inclusion of the 2-week time point allows for careful monitoring for side effects of corticosteroid treatment.

4.1.1 Types of Visits

- **Recruitment:** Following diagnosis of cholestasis in an infant ≤180 days old, the family will be approached for recruitment into the PROBE study, first, and then approached for START if the diagnosis is suggestive of or established to be BA. The subject's parent(s) or legal guardian(s) must sign a written informed consent before data collection can begin.

- **Baseline:** Once informed consent is obtained, the Clinical Research Coordinator (CRC) will abstract information from the subject's medical chart, including the physical examination at intake. The CRC will interview the subject's parent(s) or legal guardian(s) to review the child's medical history and the relevant medical history of the immediate family (this information should be captured as part of PROBE).

- **Surgery/Diagnosis:** The timeline for follow-up is triggered by the date of the portoenterostomy for subjects with biliary atresia. The surgeon will complete a Case Report Form (CRF) that describes in detail the surgical findings. The pathologist will detail the pathological findings that are relevant to the diagnosis.

- **In-patient / Discharge:** Data will be collected from the time of surgery to the time of discharge.

- **Follow-up:** Subjects enrolled in START will be followed closely during the first year post-portoenterostomy and at 18 and 24 months of age to allow for careful monitoring for side effects of the study drugs, and then will remain in follow-up for PROBE annually to 10 years of age or death, whichever comes first. However, if the subject has a transplant and is enrolled in START, the subject will be followed until age 2 in START and then continue in the study on the post-transplant followup as part of PROBE.

- **Transplant:** When a transplant is performed, samples should be collected for the repository (manifest forms). Form 26 will document the transplant surgery at the time the transplant occurs as will PROBE CRF 25N.

4.2 Case Report Form (CRF) Description and Instruction

During each outpatient visit, information will be recorded on CRFs, which are the same forms used in the PROBE (prospective observational database protocol), and on additional forms that collect information that is specific for this trial. These CRFs will capture data on the subject's physical findings, diet and medication records, laboratory findings, interval medical history, interval sentinel events, illnesses or hospital admissions, surgery, imaging follow-up, Health-Related Quality Of Life (HRQOL), ophthomology, and antibody titers to vaccines according to the protocol.

4.2.1 Baseline

4.2.1.1 Form S11 Eligibility (web-entry)

Eligibility into the START trial is determined using Form S11. This CRF is also a web-entry CRF. This form is to be completed at recruitment into START. Although the form may be completed by the CRC, the form must be signed by a Principal Investigator (PI).

Sections B and C may be completed prior to surgery.
Sections D and E must be completed with respect to the child's status after surgery.

NOTE: The data on this form must be entered into the Childhood Liver Disease Research and Education Network (ChiLDREN) website as soon as possible. The form should be sent to the Data Coordinating Center (DCC) for data entry only after all items have been answered definitively.

- ***Section A: Header Information***
  A2: Date that consent was obtained for the infant to participate in START. All data collection on CRF's for START must occur after consent is obtained.

- ***Section B: Inclusion Criteria***
  All answers in Section B must be **"Yes".**
  B1. Written informed consent to participate in the study must be obtained prior to or within 72 hours of completion of portoenterostomy. (Note: Families of potential subjects may be approached prior to the portoenterostomy). The 72 hour clock starts from the documented end time of the surgery on the portoenterostomy surgical report.

- ***Section C: Exclusion Criteria***
  All answers in Section C must be **"No".**
  C3. The exclusion criterion is that there is significant hypertension, but there is no place provided to record the blood pressure. The blood pressure can be taken any time during the preceding 24 hours and therefore should be available in

the hospital record. When this is not possible, the CRC may write the actual blood pressure on Form S11 next to the criterion and note that there is no other source document.

C4, C6-C9. These exclusion criteria apply if the subject or mother is known to have the condition. There is no requirement to test for the condition.

C10. A subject is eligible if, at the time of recruitment, the known bilirubin is in the eligible range. This bilirubin level may be from a blood draw prior to consent. The result of a blood draw after consent does not affect eligibility.

C11. A subject should not be recruited if he (or she) has concurrent illnesses or severe congenital abnormalities, such as complex cardiac disease, which places the child at high risk for complications and death.

C12. Infants who have received the live attenuated rotavirus vaccine (e.g. Rotateq) within 5 days prior to proposed administration of study drug are excluded from the study. Infants who have received the vaccine prior to this interval should not receive their first dose of steroids until a total of 5 days post vaccination has elapsed.

NOTE: These conditions also apply during the period after the portoenterostomy, but before dosing begins. Therefore, some conditions on Form S11, when present, indicate that the subject is ineligible.

- ***Section D: Post-Surgical Conditions***

D1-D2, D4. If any answer labeled "ineligible" is checked, the subject is ineligible even if the subject fulfilled the inclusion/exclusion criteria prior to surgery.

D3, D5-D6. When the response is "Yes," complete the appropriate Form S11"X" and submit that form, with the CRF, to the DCC.

D7-D8. When the response is "Yes," there is no need to complete Form S11"X".

D9. There is no requirement for an ophthalmologic exam. When an ophthalmologic examination is performed, complete Form S12J.

- ***Section E: Summary***

E1. Although exceptions/exemptions are not expected, the option is included in case there is such a case. If the subject violates an inclusion/exclusion criterion and an exemption is approved, check eligible by exemption. It is unlikely that there will be exemptions for START.

E2. Record the randomization number that you receive from the pharmacist. The randomization kit for the subject contains an envelope with the randomization number the pharmacist will give you. The number will begin with an R and have four numbers that follow. Do not record any letters (A or B) that may be listed after the number; those letters are pharmacy specific.

4.2.1.2 Randomization Process at Baseline

Randomization assignments will be performed by the DCC and either corticosteroid or placebo therapy will be initiated within 72 hours after portoenterostomy; doses will be adjusted according to the dosing schedule outlined in the protocol. The DCC will provide the central pharmacy with a list of assignments for each study site.

The list will contain:

- Study site name.
- Study site number.
- Randomization numbers.
- Corresponding drug assignment (active/placebo).

Randomization numbers will contain the study site number and then will be sequentially numbered. These numbers will serve as the kit number on the prepared kits. Study site pharmacists will be instructed to dispense kits to subjects sequentially.

4.2.1.3 Drug Kit Assignment at Baseline

Kits will be prepared based on the randomization assignments provided to the central pharmacy by the DCC. Each kit will have a unique number, which corresponds to the drug assignment (active or placebo).

Study medication, as well as, kit boxes will be labeled by Central Pharmacy (CCHMC IDS). Labels will also be provided to study site pharmacies for labeling dispensed study medication. These labels contain the minimum requirements. It is the study site's responsibility to ensure that study medication is labeled according to their institution's requirements. Samples of all labeling are located in the pharmacy Manual Of Operations (MOO).

4.2.1.4 Administration of Study Drug or Placebo at Baseline

Randomization will be performed by the DCC and either corticosteroid or placebo therapy will be initiated within 72 hours after portoenterostomy; doses will be adjusted according to the dosing schedule outlined below. Corticosteroids or placebo will be given via intravenous (IV) for at least 2 post-operative days or until the infant resumes oral or enteric feedings. When the infant is tolerating oral or enteric feedings, prednisolone or placebo will be given orally for the remainder of the course of study drug/placebo as indicated in Table 1. Compounding of placebo by a registered pharmacist will match the corticosteroid product for appearance and taste.

Table 1. Schedule and Dosing of Corticosteroids or Placebo Following Portoenterostomy in Infants with Biliary Atresia.

Day/Week of Dosing	Corticosteroids[1]	Placebo
Days 1-7		

--days 1-3 --days 4-7	Methylprednisolone, IV – 4 mg/kg/day, divided BID Prednisolone, PO – 4 mg/kg/day, divided BID	IV – Normal saline (same volume, BID) PO – Placebo (same volume, BID)
Week 2	4 mg/kg/day, divided BID	PO same volume BID
Week 3	2 mg/kg/day, divided BID	PO same volume BID
Week 4	2 mg/kg/day, divided BID	PO same volume BID
Week 5	1 mg/kg/day, once a day	PO once a day
Week 6	1 mg/kg/day, once a day	PO once a day
Week 7	0.8 mg/kg/day, once a day	PO once a day
Week 8	0.6 mg/kg/day, once a day	PO once a day
Week 9	0.4 mg/kg/day, once a day	PO once a day
Week 10	0.2 mg/kg/day, once a day	PO once a day
Week 11	0.1 mg/kg/day, once a day	PO once a day
Week 12-13	0.1 mg/kg/every other day	PO every other day
Week 14	Stop	Stop

[1]Initial dosage will be based on subject's weight. Subsequent doses will be adjusted based on subject's weight measured monthly at each scheduled outpatient visit.
Abbreviations: BID = Twice daily; IV = Intravenous; PO = Orally.

4.2.1.5 Adjunct Medications and Treatment at Baseline (ursodiol, vitamin K, AquADEK™, TMP-SMZ (Bactrim), ranitidine (Zantac®))

Post-operatively and at time of randomization, it is the responsibility of the study team to inform the providers caring for the subject about the subject's participation in the trial. For example, post-op, the subject may be on the Surgery Service. Therefore, many study sites need to provide information about the study to the surgery residents as they have responsibility for the subject. Surgery residents change frequently as they rotate off service; so make sure the PI and CRC contact numbers are given and placed somewhere readily available (i.e.; in the very front of the medical record).

Orders for IV study medication (steroid vs. placebo) should be written and dispensed. Prescriptions for all additional medication (ranitidine, vitamins, etc.) should be written by a PI in accordance with each institution's policy. These prescriptions will be filled from the bulk supply of medication provided to the study site pharmacies from the central pharmacy.

All orders need to be signed in a manner compliant with the local Institutional Review Board (IRB), usually by an investigator who is listed on the IRB application and listed in the 1572. As is well-recognized, the PI is ultimately responsible.

Medications Prior to Toleration of Oral/Enteric Feedings

- **IV medications:** IV medications should be given for at least 2 days post-op or until the subject is able to tolerate oral feedings. IV antibiotics are routinely used postoperatively at ChiLDREN study sites as prophylaxis against ascending cholangitis. The choice of IV antibiotics will be according to the local standard of care.

- **H2 blocker or proton pump inhibitor:** Postoperatively, subjects will receive IV medication to suppress gastric acid production (H2 blocker or proton pump inhibitor, according to the local standard of care) until they resume oral/enteric feedings.

Medications Once Tolerant of Oral/Enteric Feedings

- **Ranitidine (Zantac®):** Once subjects resume oral/enteric feedings, they will receive 12.5 mg twice daily (BID) oral ranitidine (Zantac®) (2-6 mg/kg/day, see Section 4.M.7 of the protocol), provided by the study, while receiving steroid/placebo; ranitidine (Zantac®) is approved by the FDA for use in children (1 month-16 years of age).

- **Trimethoprim-Sulfamethoxazole (TMP-SMZ) (Bactrim):** Once oral/enteric feedings are tolerated, oral TMP-SMZ (Bactrim) (4-5 mg TMP/kg/day) provided by the study will be initiated and continued up to 6 months. In the event of the occurrence of an episode of cholangitis, despite antimicrobial prophylaxis, subjects will be treated with parenteral antibiotics according to the standard of care at the study site where the subject is enrolled. Thereafter, prophylaxis with oral TMP-SMZ (Bactrim) will be used for 6 months.

  In addition to serving as prophylaxis against ascending cholangitis for all subjects, this regimen will also provide prophylaxis for pneumocystis carinii pneumonia (PCP) in subjects receiving corticosteroids. In the unlikely event that the subject develops a hypersensitivity reaction to TMP-SMZ (Bactrim) manifested as a skin rash, the medication will be discontinued promptly and oral neomycin (25/mg/kg twice a day orally) will be used for prophylaxis against ascending cholangitis.Because neomycin provides no prophylaxis against PCP, the subject will also undergo a blinded taper and discontinuation of the study drug/placebo as outlined in the protocol. The cost of the neomycin should be covered by each study site's grant (subject cost).

Other Medications or Supplements

The protocol is not explicit about the start date for the other medications (Urso, AquADEK™, and mephyton), except that the subject should be receiving the other medications when released home. Therefore, the medications and vitamins can be started before hospital discharge when this is the local standard of care or, the medications can be started when oral feedings resume.

The other study-supplied medications or supplements are as follows:

- ***Ranitidine (Zantac®):*** 12.5 mg twice daily for 3 months (i.e. during the study drug taper).

- ***TMP-SMZ (Bactrim):*** 4-5 mg TMP/kg/day for 6 months.

- ***Ursodeoxycholic acid (Urso® suspension):*** 20 mg/kg/day divided into 2 doses per day.

- ***AquADEK™ vitamin drops:*** 2 mL daily until total bilirubin <1.5 mg/dL or age 2 years.
  NOTE: Effective 8/25/2010
  Axcan will no longer supply AquADEK™ for the START trial. After assessing costs and feasibility of procuring AquADEK™ centrally versus at the study site level, the ChiLDREN Executive Committee has decided that the best course of action is for each study site to purchase AquADEK™ locally for START subjects. Each study site should have a documented plan from where the AquADEK™ will be purchased. Study sites responding to queries have confirmed that AquADEK™ is readily available from the local clinical pharmacy.

  Despite the change in supplier, AquADEK™ remains a study medication and is an integral component of the START protocol. Current practices of accountability tracking should remain in effect and are specified in 4.3.2-3. A study site research pharmacy should continue to be responsible for inventory and management of the materials while stored at the study site pharmacy. If a study site's pharmacy staff have questions, instruct them to contact the DCC.

  Costs associated with purchasing AquADEKs can be considered patient care costs and should be managed through the local site budget. The Executive Committee recognizes this expense as 'new' for each study site and that in the case of high-enrolling centers, the expense may be significantly higher than other sites. If potential budget impact is a concern at a specific study site, contact Dr. Pat Robuck to work directly on locating needed funds.

- ***Vitamin K:*** 2.5 mg co-administered with AquADEK™ on Mondays, Wednesdays and Fridays.

- ***Pregestimil:*** With respect to feeding, mothers who are *breastfeeding* are encouraged to continue. If supplementation is needed, the Medium Chain Triglyceride (MCT)-containing formula Pregestimil is provided by the study. *Formula-fed* infants are given Pregestimil until their total bilirubin is less than 1.5 g/dL. Additional nutritional supplementation is individualized based on each infant's growth pattern.

4.2.1.6 Discharge to Home Information

At time of discharge from hospital following portoenterostomy, there are START-specific CRFs that need to be completed, in addition to the PROBE discharge CRFs.

- ***Form S12 Discharge AE Screen:*** This form should be completed and signed by the PI. When the response is "Yes," to any of the screening questions, complete the appropriate Form S12"X" and submit that form with the CRF to the DCC.

- ***Form 12 Hospital Discharge (section S)****:* The medications in this section refer to those given during hospitalization.
  - *Laboratory evaluation***:** These additional labs must be drawn prior to discharge from the hospital. Results are recorded on this form.
  - *Medication addendum***:**
    S37. Report the number of days for IV antibiotics. There is no need to provide doses.
    S45. Report non-START medications that were given during hospitalization in section S45, including antibiotics used peri-operatively (per direction of Steering Committee (SC). If needed, use additional sheets.

- ***Form 13 Discharge Medications:*** The medications on Form 13 refer to those prescribed at discharge. Do not record the dosages of the study-supplied medications given to the subject. This includes the dosages for ursodiol, TMP-SMZ (Bactrim), steroid, ranitidine (Zantac®), vitamin k, and AquADEK™. These medications are recorded on the appropriate Form S13"X" medication form.

At time of discharge, make sure the subject has received all of their study-supplied medications, Pregestimil, medication diary, and instructions about the medications and their participation in the study. It is recommended that a letter is sent to the child's pediatrician informing the primary care doctor about the child's participation in the study. The letter should also mention the recommendation that vaccines be withheld during the first 4 weeks when the study drug/placebo is taken.

4.2.2 2-Week Follow-Up Visit

Following portoenterostomy and discharge from the hospital, subjects will be evaluated in the outpatient clinic 2 weeks after portoenterostomy. The inclusion of the 2-week time point will allow for careful monitoring for side effects of corticosteroid treatment. This follow-up visit is only for subjects enrolled in the steroid trial.

Study medication should not be re-dosed/re-prescribed at this visit unless there is a clinical indication to do (i.e. subject had a dramatic drop in weight).

START-specific forms associated with the 2-week follow-up visit include:

- ***Form 20.2WK Two-Week Follow-Up Physical Exam:***
  B1. A Doppler instrument will be used to measure Blood Pressure (BP). BP measurement should begin after 5 minutes of rest and when the infant is quiet. A bladder width measuring 6 cm (infant size) will be used. The infant will be supine with the right arm resting on a supportive surface at the heart level. Two BP readings will be obtained and separated by 2 minutes. The readings will be averaged. If the first two readings differ by more than 5 mm Hg, additional readings will be obtained and averaged.

- ***Form S20 AE Screening:***
  - Form S20 is only completed if the subject has been enrolled in START. This form should be completed at each visit, even after study medication has stopped. If subject is no longer taking steroid/placebo, skip the items describing dose adjustments on Form S20"X".
  - When appropriate, findings on the AE Screening should also be reported on **Form(s) 22** (Follow-up diet and medications), **25-27** (sentinel events and imaging) and/or **45** (SAE).
  - A2. Enter date of the physical exam. This date should usually be the date on Form 20. When the response is "Yes" to any of the screening questions, complete the appropriate Form S20"X" and submit that form with the CRF to the DCC.

- ***Form S22.2WK Two-Week Follow-Up Diet and Medications:***
  - The study will provide diaries for the subject's parent(s) or legal guardian(s) to help keep track of the medical visits and changes in their child's medication that have occurred between START trial visits. Review this diary at each visit and copy all changes in medications onto the CRF.
  - C1. Ask about all (other than study medications) vitamins and supplements that the child has taken since discharge from the hospital.
  - D1. Ask about all other prescription medications that the child has taken since discharge from the hospital.

- ***Form S23.2WK Two-Week Follow-Up Labs***

- ***Form[Bilirubin] (Effective 7/14/2010):***
  - Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
  - Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
  - Instructions (available on web-entry screen):
    Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-

pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

NOTE: The DCC has a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Forms S20B-F; 24-27 (as needed):*** Use the forms from the 1-month visit when reporting events.

4.2.3 1-Month Follow-Up Visit

At the 1-month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START-specific forms associated with the 1-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** Study-supplied medications should be prescribed and dispensed. The subject's parent(s) or legal guardian(s) should be instructed to return all empty study-supplied medications. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***
  - Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
  - Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
  - Instructions (available on web-entry screen):
    Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

NOTE: The DCC has a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Manifest Form 90 Vitamin levels:*** Vitamins levels should be drawn at this visit. The subject's parent(s) or legal guardian(s) should be instructed prior to the appointment to withhold giving the morning dose of vitamins and to withhold formula/breast milk 4 hours prior to laboratory testing. See section on vitamin testing for specific information. Results from this testing is recorded on CRF 23.

4.2.4 2-Month Follow-Up Visit

At the 2 month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START specific forms associated with the 2-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** Study-supplied medications should be prescribed and dispensed. The subject's parent(s) or legal guardian(s) should be instructed to return all empty study-supplied medications. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form. See instructions on completing Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***
  - Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
  - Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
  - Instructions (available on web-entry screen):
    Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

NOTE: The DCC has developed a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Form 90 Vitamin levels:*** Vitamins levels should not be drawn at this visit unless there was a dose modification the previous month. See section on vitamin testing for specific information.

4.2.5 3-Month Follow-Up Visit

At the 3 month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START-specific forms associated with the 3-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** Study-supplied medications should be prescribed and dispensed. The subject's parent(s) or legal guardian(s) should be instructed to return all empty study-supplied medications. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form S23a. See instructions on completing Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***
  - Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
  - Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
  - Instructions (available on web-entry screen):
    Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

NOTE: The DCC has developed a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Forms S34C/M/F/H/S [Knowledge of Treatment Assignment]:*** The START study requires that the subject's parent(s) or legal guardian(s), hepatologist, surgeon, PI, and CRC complete a questionnaire. The purpose of this form is to evaluate the staff and the subject's parent(s) or legal guardian(s) to assess if they have conjectured regarding whether the subject is receiving corticosteroids or placebo.

  These forms are completed only at the 3 month visit. Each individual will receive the form with an envelope provided by the CRC. The CRC will instruct each individual to complete form and seal in the envelope. The purpose of the data being sealed in an envelope is to eliminate bias among responses. The CRC will collect the envelopes and will ship in the sealed envelopes to the DCC. **NO** copies of these forms (including that of the CRC) will be kept at the study site. The exception to this is when sites send their CRFs electronically. In this case, it is appropriate for the coordinator to send the forms electronically rather than mail them in sealed envelopes.

  If subject has been unblinded during the treatment phase:
  When the child has been unblinded for any reason, the required individuals do **NOT** have to complete this form. The CRC will check the "Yes" box for the question regarding if the unblinding envelope has been opened and will send all the forms to the DCC.

  - *Form S34C Knowledge of Treatment Assignment Coordinator*: Form S34C is to be completed by the *CRC*. It has different instructions than the other 34"X" forms. The CRC's form is not seen by anyone else prior to shipment to the DCC and therefore does **NOT** have to be sealed in an envelope nor do the CRCs have to keep a copy of Form S34C in the research binder.

    Section D of S34C: Once the subject's parent(s) or legal guardian(s), hepatologist, and surgeon have returned their sections of Form S34, the CRC must complete Section D on S34C. If any answer is "No", specify the reason.

  - *Form S34M Knowledge of Treatment Assignment Mother*: To be completed by the *mother* or *primary guardian*. It is anticipated that the form will only be completed by the subject's parent(s) or legal guardian(s) who bring the child to the 3-month clinic visit. Therefore, check NA if a subject's parent or legal guardian did not attend the visit.

  - *Form S34F Knowledge of Treatment Assignment Father*: To be completed by the *father* or *second guardian*. It is anticipated that the form will only be completed by the subject's parent(s) or legal guardian(s) who bring the child to the 3-month

clinic visit. Therefore, check NA if a subject's parent or legal guardian did not attend the visit.

- o *Form S34H Knowledge of Treatment Assignment Hepatologist*: To be completed by the *hepatologist.* This form is only applicable to a hepatologist or surgeon who interacts with the subject. Although it is anticipated that there will always be a hepatologist who will interact, check NA when the hepatologist or surgeon did not have much contact with the subject.

- o *Form S35S Knowledge of Treatment Assignment Surgeon*: To be completed by the *surgeon.* This form is only applicable to a hepatologist or surgeon who interacts with the subject. Although it is anticipated that there will always be a hepatologist who will interact, check NA when the hepatologist or surgeon did not have much contact with the subject.

- ***Manifest Form 90 Vitamin levels:*** Vitamins levels should be drawn at this visit. The subject's parent(s) or legal guardian(s) should be instructed prior to the appointment to withhold giving the morning dose of vitamins and to withhold formula/breast milk 4 hours prior to laboratory testing. See section on vitamin testing for specific information.

4.2.6 6-Month Follow-Up Visit

At the 6 month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START-specific forms associated with the 6-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** The subject comes off of the study-supplied TMP-SMZ (Bactrim) medication at the 6-month follow-up visit. Study-supplied medications should be prescribed and dispensed. The subject's parent(s) or legal guardian(s) should be instructed to return all empty study-supplied medications. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form 23a. See instructions on completing Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***

- Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
- Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
- Instructions (available on web-entry screen):
  Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

  NOTE: The DCC has developed a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Manifest Form 90 Vitamin levels:*** Vitamins levels should be drawn at this visit. The subject's parent(s) or legal guardian(s) should be instructed prior to the appointment to withhold giving the morning dose of vitamins and to withhold formula/breast milk 4 hours prior to laboratory testing. See section on vitamin testing for specific information.

4.2.7 12-Month Follow-Up Visit

At the 12 month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START-specific forms associated with the 12-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** Study-supplied medications should be prescribed and dispensed. The subject's parent(s) or legal guardian(s) should be instructed to return all empty study-supplied medications. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Form S20J Cataracts:*** In addition to the PROBE-specific data collection elements (i.e. developmental testing, whole blood for genetics), subjects enrolled in START should undergo ophthalmologic evaluation to screen for cataracts at the 12-month follow-up visit. The exam will be performed for all subjects enrolled in START, even if the child did not complete the full 13 weeks of treatment (placebo/steroid). The

ophthalmologic examination at 12 months is paid for by the research grant. The CRC should document the eye exam results on the 12M ophthalmology exam form which is located in Form S20 AE Screening.

- *Cataracts*
  Cataracts are a well-recognized complication of long-term corticosteroid therapy, and are related both to dosage and duration of therapy. Children appear to be particularly at risk for steroid-induced cataracts. Despite the relative short duration of corticosteroid treatment in this clinical trial, all subjects will undergo an ophthalmologic examination at 12 months of age to monitor for the development of corticosteroid-induced posterior subcapsular cataracts. The examination will be performed by a pediatric ophthalmologist. The incidence of cataracts in corticosteroid treated-subjects and in placebo controls will be reported to the Data and Safety Monitoring Board (DSMB).
- *Red Reflex*
  Examination for a red reflex is to be performed by a pediatrician. When the result is abnormal, the pediatrician should consider asking for an ophthalmologic consult as part of usual clinical care.

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form 23a. See instructions on completing Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***
  - Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
  - Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
  - Instructions (available on web-entry screen):
    Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

    NOTE: The DCC has a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Manifest Form 90 Vitamin levels:*** Vitamins levels should be drawn at this visit. The subject's parent(s) or legal guardian(s) should be instructed prior to the appointment to withhold giving the morning dose of vitamins and to withhold formula/breast milk 4 hours prior to laboratory testing. See section on vitamin testing for specific information.

4.2.8 18-Month Follow-Up Visit

At the 18-month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START-specific forms associated with the 18-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** Study-supplied medications should be prescribed and dispensed. The subject's parent(s) or legal guardian(s) should be instructed to return all empty study-supplied medications. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Form S22I 18 Month Immunization Record:*** At 18 months of age or at the time of liver transplantation (if younger than 18 months of age), the vaccination records of each subject will be obtained from the primary care provider for review. The number and size of doses, dates of administration, and vaccine manufacturer will be recorded.

- ***Form S22V 18 Month Vaccine Titers:*** At the age of 18 months, 6-9 ml of blood will be obtained to measure serum antibody titers against individual vaccine antigens. The antibody titers will be measured by the study sites local laboratory. Priority titers to be collected relate to vaccinations for Hepatitis B, Tetanus, and Polio.
  - If a subject has received a transplant before the 18-month visit, titers should **NOT** be collected.
  - If serum antibody titers do not achieve protective levels as determined by the local laboratory standard and the investigator, the information will be provided to the primary care provider so that booster/re-immunization of appropriate antigen(s) is given. Absent titers will also be communicated to the primary care provider, who will treat with re-immunization as directed by the American Academy of Pediatrics (AAP) guidelines for catch-up immunization. The CRC should maintain a record that indicates that the primary care provider was contacted when absent titers or non-protective levels are resulted.

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form 23a. See instructions on completing Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***

- Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
- Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
- Instructions (available on web-entry screen):
  Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

  NOTE: The DCC has developed a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Manifest Form 90 Vitamin levels:*** Vitamins levels will be drawn at this visit only if the subject continues on AquADEK™ to maintain adequate serum levels of fat-soluble vitamins or if a dose change had been made during the previous visit. If a subject is no longer receives the vitamin supplementation because the total bilirubin concentration is <1.5 mg/dL, the vitamin concentrations will not be checked at 18 months of age. See section on vitamin testing for specific information.

4.2.9 24-Month Follow-Up Visit

At the 24-month follow-up visit, the majority of CRFs are completed as part of PROBE. See section on post-transplant for a list of CRFs that are completed at study visits. These instructions are for the START subject who is not transplanted.

START-specific forms associated with the 24-month follow-up visit include:

- ***Forms S13B-H [Study Medications]:*** Study supplied medications should be returned at this visit and no additional medications are dispensed through the study, as participation is ended. Medication reconciliation should be performed following the visit and recorded on the appropriate S13 form. See instructions on completing S13 CRFs.

- ***Form 20 Physical Exam:*** Vital signs must be completed as part of START. If not completed, a protocol deviation form should be filled out.

- ***Form 21A Pediatric Quality of Life (PedsQL) Inventory Toddlers (ages 2-4) (as applicable):*** If the subject underwent liver transplantation prior to the 24-month follow-up visit, complete Form 21A as part of the START trial; for subjects alive with

or without transplant after exiting START, this information should be captured as part of PROBE

- ***Form 21C Results of Bayley-II (ages 1 and 2) (Effective 02/01/2010):*** Study sites should switch to use of Bayley III instrument immediately for neurodevelopment assessment. For those subjects who are already enrolled in the PROBE study and have had the Bayley II administered at age 1; administer the Bayley II at age 2. Those subjects that are either 1. new to the PROBE study or 2. have not had the Bayley II administered; adminster the Bayley III at age 1 and at age 2. If Bayley II testing/scoring materials are not available at the study site, contact the DCC (children-dcc@umich.edu) for shipment of the necessary testing materials. If the subject underwent liver transplantation prior to the 24-month follow-up visit, complete Form 21C as part of the START trial; for subjects alive *with or without transplant after exiting START,* this information *should be* captured as part of PROBE

- ***Forms 23 and S23.2WK [Follow-Up Labs]:*** Bilirubin must be obtained at each START research visit. In addition to Form 23, the result must also be recorded on Form S23a. See instructions on completing Form S23a.

- ***Form S23a [Bilirubin] (Effective 7/14/2010):***
  - Web-entry only form. To be completed at ***ALL*** START visits, where the total bilirubin is required/obtained. Per previous procedure, bilirubin results continue to be documented on Forms 8, 23 and S23.2WK.
  - Developed to ensure that the total bilirubin is obtained and reported by the study site's laboratory at the time-points specified in the protocol – primarily at the 6 month time-point for those with their native liver (primary endpoint of the study).
  - Instructions (available on web-entry screen):
    Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

    NOTE: The DCC has developed a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Forms S35 Final Status and Form 35 Final Status (as applicable):*** Regardless of whether the subject survived with native liver, discontinued from study drug, or received a liver transplant, at the 24-month follow-up visit, all subjects are exited from the START trial. Form S35 Final Status (web-entry and paper CRF) will be used to exit subjects from the trial.
  - If the subject is exiting both PROBE (i.e. death or lost to follow-up) and START, complete Forms S35 Final Status and Form 35 Final Status.

- If the subject will continue with the PROBE study only complete S35 (paper and web-based).

- ***Manifest Form 90 Vitamin levels:*** Vitamins levels should be drawn at this visit. The subject's parent(s) or legal guardian(s) should be instructed prior to the appointment to withhold giving the morning dose of vitamins and to withhold formula/breast milk 4 hours prior to laboratory testing. See section on vitamin testing for specific information.

- ***Developmental Testing and PedsQL:*** Developmental testing is primarily conducted as part of the research subject's participation in the PROBE study. Information on specific developmental testing and time points for this testing can be found in the PROBE MOO. At the 24-month follow-up visit, developmental testing and PedsQL will be completed for those subjects in the trial who either: a) have survived with native liver or b) were transplanted.
  - If a START subject is transplanted prior to their 1 or 2 year birthdays, though no longer participating in pre-transplant part of PROBE, they would return for their developmental testing at both these time points as part of their participation in the START trial. (If subject is transplanted prior to their 1 year birthday, they will return for developmental testing at both 1 and 2 year as part of START).

4.2.10 Study-Specific Procedures for Subjects Undergoing Liver Transplantation Prior to 2 Years of Age

Should a START subject undergo liver transplantation prior to 2 years of age, the subject is not exited from the START trial until 2 years of age.

The following procedures should continue to be collected at the visit when the information is typically collected. The data collected post transplant is limited and does not involve all of the CRFs typically used as part of PROBE/START.

- Knowledge of Treatment Assignment (Form S34s) at 3-month follow-up visit (if not yet completed).
- Cataracts (Form S20J) at 12-month follow-up visit (if not yet completed).
- Developmental testing up to age 2 (i.e. age 1 and 2 years).
- 18 Month Immunization Record (Form S22I) at 18-month follow-up visit.
- 18 Month Vaccine Titers (Form S22V) at 18-month follow-up visit. Do **NOT** collect if the subject has received a liver transplant before the 18-month follow-up visit.
- Protocol Deviation (Form 40), as applicable.
- Genetics (Manifest 49C) at 1 year of age (if not yet completed).

Do **NOT** collect the following for post-transplant subjects at visits that occur post-transplant:

- No Need to continue supportive research medications.
- Do not collect plasma, serum, or urine.
- Do not collect vitamin levels.
- Do not collect vaccine titers.
- Do not collect physical exam findings
- Do not collect laboratory data
- Do not collect sentinel events
- Do not collect SAEs post-transplant.

4.2.11 Important CRFs Used Throughout the START Study

- ***Form 23a Bilirubin (web-entry)***

Form S23a is a web entry form developed to ensure that the Total Bilirubin is obtained and reported by your laboratory at the time-points specified in the protocol. This form should be completed at ***ALL*** START visits, where the Total Bilirubin is required/obtained (2 week, 1 month, 2 month, 3 month, 6 month, 12 month, 18 month, 24 month, transplant).

Bilirubin results are still documented onto **Forms 8** (Initial Labs)**, 23** (Follow-Up Labs) and **S23.2WK** (2-week Follow-Up Labs).

Instructions:

Total bilirubin MUST be reported for all START subjects within 72 hours of receipt of the actual laboratory results. The source document laboratory results (with PHI removed) MUST be emailed to DCC project managers (children-pm@umich.edu) (preferred) OR faxed to (734) 647-3711 or. Emailed documents must be password-protected.

NOTE: The DCC has developed a system to notify study site via e-mail that a subject is due for their visit or almost out of the visit window. This notification will aid in ensuring that the total bilirubin is not missed for these required visits.

- ***Forms S13B-H [Study Medications]***

  - *S13 B Steroid/Placebo (web-entry):* This form can be found by opening the subjects electronic study book and navigating to the diagnosis/surgery section of the study book. Comments regarding any of the items can be provided in the comments section.

    Section B: Record the dosages prescribed and taken throughout the 14 week course. Indicate whether the dose was taken parentally or orally, the total mg/day, the date the dose was started and the date the dose ended. Add your

initials and save. Once saved, a new line will appear to record the next part of the taper.

Section C: Used to assess the compliance with the study medication. In the "Dispensed" columns, enter the date the medication was dispensed and the volume in mLs. Add your initials.
In the 'Returned" column:

- If the medication has <u>not</u> been returned yet because the subject still has the bottle, then mark "Pend" and save.
- If the bottle will not be returned because it was lost, for example, mark "No" and compliance will not be assessed for that bottle.
- If the bottle has been returned and compliance can be assessed, enter the date the medication was returned. Enter the actual amount that was returned and the amount that was expected to be returned. In some cases, the actual will be less than the expected amount when the subject's parent(s) or legal guardian(s) have to give more of the medication because of spilling or if the dose is spit-up.

Signatures: When the study medication taper is completed and all data have been entered, change the site signature line to "Yes", add the date the form was completed, and print out the form. The form should then be signed by the PI or CRC and stored in the subject's study binder.

- <u>*S13 C Steroid Pulse:*</u> In the unlikely event a steroid pulse is needed, this form should be used to describe the dose and tapering procedure that was prescribed.

- <u>*S13 D Ranitidine:*</u> When the subject stops using this medication, send a copy of this form to the DCC.

Section B: List the prescribed dosages (total daily) and the start date and end date for each dose.

Section C: The log should be kept as number of tablets dispensed or returned. Use one line for each bottle (container) that is dispensed. List the date and amount dispensed, as well as CRC's initials. When the bottle (container) is returned, enter the date and the amount returned, as well as CRC's initials.

Compliance is defined as the child having taken 80% of the dose that was prescribed for the period. Estimate whether the number of tablets used is consistent with at least 80% compliance with the dose prescribed. If so, check "Yes" for compliance; otherwise, check "No".

When the subject's parent(s) or legal guardian(s) provide a reason for the discrepancy in the amount returned, enter the reason as a comment. Enter the item identifier for the line at the beginning of the comment so that the comment can be associated with a specific bottle (container).

- *S13 E TMP-SMZ (Bactrim):* When the subject stops using this medication, send a copy of this form to the DCC.

  Section B: List the prescribed dosages (total daily) and the start date and end date for each dose.

  Section E: Use one line for each bottle (container) that is dispensed. List the date and amount dispensed as well as the CRC's initials. When the bottle (container) is returned, enter the date and the amount returned, as well as the CRC's initials.

  Compliance is defined as the child having taken 80% of the dose that was prescribed for the period. Estimate whether the amount of volume used is consistent with at least 80% compliance with the dose prescribed. If so, check "Yes" for compliance; otherwise, check "No".

  When the subject's parent(s) or legal guardian(s) provide a reason for the discrepancy in the amount returned, enter the reason as a comment. Enter the item identifier for the line at the beginning of the comment so that the comment can be associated with a specific bottle (container).

- *S13 F Urso:* When the subject stops using this medication, send a copy of this form to the DCC.

  Section B: List the prescribed dosages (total daily) and the start date and end date for each dose.
  Section F: Use one line for each bottle (container) that is dispensed. List the date and amount dispensed, as well as the CRC's initials. When the bottle (container) is returned, enter the date and the amount returned, as well as the CRC's initials.

  Compliance is defined as the child having taken 80% of the dose that was prescribed for the period. Estimate whether the amount of volume used is consistent at least 80% compliance with the dose prescribed. If so, check "Yes" for compliance; otherwise, check "No".

  When the subject's parent(s) or legal guardian(s) provide a reason for the discrepancy in the amount returned, enter the reason as a comment. Enter the item identifier for the line at the beginning of the comment so that the comment can be associated with a specific bottle (container).

- *S13 G – AquADEK™:* When the subject stops using this medication, send a copy of this form to the DCC.

Section B: List the prescribed dosages (total daily) and the start date and end date for each dose.

Section G: Use one line for each bottle (container) that is dispensed. List the date and amount dispensed, as well as the CRC's initials. When the bottle (container) is returned, enter the date and the amount returned, as well as the CRC's initials.

Compliance is defined as the child having taken 80% of the dose that was prescribed for the period. Estimate whether the amount of volume used is consistent at least 80% compliance with the dose prescribed. If so, check "Yes" for compliance; otherwise, check "No".

When the subject's parent(s) or legal guardian(s) provide a reason for the discrepancy in the amount returned, enter the reason as a comment. Enter the item identifier for the line at the beginning of the comment so that the comment can be associated with a specific bottle (container).

- *S13 H – Vitamin K:* When the subject stops using this medication, send a copy of this form to the DCC.

  Section B: List the prescribed dosages (total daily) and the start date and end date for each dose.

  Section H: Use one line for each bottle (container) that is dispensed. List the date and amount dispensed, as well as the CRC's initials. When the bottle (container) is returned, enter the date and the amount returned, as well as the CRC's initials.

  Compliance is defined as the child having taken 80% of the dose that was prescribed for the period. Estimate whether the amount of volume used is consistent at least 80% compliance with the dose prescribed. If so, check "Yes" for compliance; otherwise, check "No".

  When the subject's parent(s) or legal guardian(s) provide a reason for the discrepancy in the amount returned, enter the reason as a comment. Enter the item identifier for the line at the beginning of the comment so that the comment can be associated with a specific bottle (container).

4.3 Pharmacy Dispensing of Study Medications

4.3.1 Dispensing Steroid/Placebo

Prescriptions for study medication should be written by an investigator in accordance with each institution's policy. Study medication should be filled, dispensed by the study site research pharmacist on a monthly basis and labeled per institution policy.

- Weeks 1 through 4 are dispensed at baseline visit; weeks 5 through 8 are dispensed at the 1-month follow-up visit; and weeks 9 through 13 are dispensed at the 2-month follow-up visit.
- Dosing will be adjusted according to the infant's weight. Any changes in dosage will be communicated to the DCC on the CRFs, and to the family by the CRC.
- Labels for the study medication are provided and contain the minimum requirement. These labels will be yellow in color to help distinguish the study medication from all other medications.

1. ***Obtain kit:*** When a subject is enrolled in the trial, the study site pharmacist will obtain the appropriate kit. Each kit will contain enough medication for the entire course of treatment. In the event a kit does not contain enough study medication, the study site pharmacist will contact the central pharmacy for instructions. Kits will be dispensed sequentially.

2. ***Drug assignment:*** The pharmacist should retrieve the white "assignment envelope" from the kit. The contents of the envelope will be removed. The pharmacist reads the drug assignment for the IV portion of the trial from the yellow card. The pharmacist completes the blue label with subject identifier and gives it to the CRC to be placed on the CRF. The blue label contains the kit number and subject identifier only. The yellow card should be returned to the envelope and placed inside the kit.

3. ***Filling:*** When a subject is able to tolerate oral intake, the pharmacist will dispense study medication from the assigned kit number to the subject. The pharmacists will withdraw the appropriate volume of drug to be administered.

4. ***Labeling:*** Each study site will label per institution's policy. Label must state "methylprednisolone ___ mg OR Placebo" in order to maintain the double-blinded nature of the study.

5. ***Dispensing:*** An appropriate quantity for the subject's dose should be dispensed at each visit. Upon initial dispensing to a subject, a study drug information sheet should be supplied to the subject, either from the pharmacist or the CRC. The subject's parent(s) or legal guardian(s) should be trained on providing the medications before the subject is discharged from the hospital.

4.3.2 Dispensing Other Study Medications

Prescriptions for all additional medication (ranitidine, vitamins, etc.) should be written by an investigator in accordance with each institution's policy. These prescriptions will be filled from the bulk supply of medication provided to the study site pharmacies from the central pharmacy.

All orders need to be signed in a manner compliant with the local IRB, usually by an investigator who is listed on the IRB application and listed in the 1572. As is well-recognized, the PI is ultimately responsible.

- The subject should transition to the study-supplied oral ranitidine (Zantac®) and TMP-SMZ (Bactrim) when the standard of care H2 blocker and antibiotic are discontinued.
- The protocol is not explicit about the start date for the other medications (Urso, AquADEK™, and mephyton), except that the subject should be receiving the other medications when released home. Therefore, the medications and vitamins can be started before hospital discharge (when this is the local standard of care).

4.3.3 Subject Drug Accountability

This study will document dispensing, return, actual amount prescribed, and compliance of all study medications.

Compliance is defined as the child having taken 80% of the dose that was prescribed for the period. Estimate whether the amount of volume used is consistent with at least 80% compliance with the dose prescribed.

Each medication provided by the study has a corresponding Form S13"X". These forms will be used to document the dispensing, return, actual amount prescribed, and compliance of all study medications.

Note: Only Form S13B is web-entry; all other Form S13"X" are available on the website for printing.

4.4 Dose Reductions

In the event that a subject has a potential expected or unanticipated side effect of the study drug/placebo (such as irritability), but there is no indication to stop the study drug/placebo, the PI will have the option to reduce the dose of the study drug/placebo by 50%. The subject will then be monitored for improvement in these symptoms.

- If the symptoms improve within 48 hours, the subject will be maintained at the reduced dose for the remainder of the days planned for the original dose, as well as for the duration of treatment with this dose according to the normal taper schedule (Table 2).
- If symptoms do not improve/resolve, a further reduction by 50% of the new dose will be considered by the PI. Any reduction in the dosage of study drug/placebo will be reported to the DCC by the PI, along with the notification of the Adverse Event (AE).

- If the symptoms persist beyond 48 hours and the PI judges it necessary that the study drug/placebo be discontinued, the tapering and discontinuation protocol outlined below will be followed.

4.5 Tapering

4.5.1 Blinded Taper

If a Serious Adverse Event (SAE) (see definition in Section 7.B3 of protocol) is documented and thought by the PI to be possibly related to the study drug/placebo or if the subject withdraws from the study before the completion of the study drug/placebo, the PI will initiate a blinded taper of the study drug/placebo following the schedule outlined in Table 2. The taper will be implemented in a blinded fashion in order to maintain objectivity in subject care and data collection during follow-up visits for the duration of the study.

Table 2: Tapering Protocol for Discontinuation of Study Drug or Placebo

Duration of Treatment	Plan
Week 1	No need to taper; discontinue study drug or placebo.
Weeks 2-8	Decrease dose to 0.6 mg/kg/day study drug/placebo orally x 7 days. Then decrease the dose by 50% x 7 days and stop.
Weeks 9-10	Decrease the dose by 50% for 7 days and stop.
Weeks 11-13	Stop without taper.

4.5.2 Unblinded Taper

In the event of a life-threatening complication and when the physician treating the subject determines that knowing whether the subject was taking corticosteroid is essential to implement his (or her) treatment plan (e.g., need for stress dose of steroid in the setting of bacteremia and hypotension or invasive tissue sepsis with systemic symptoms), the study code will be broken to reveal if the subject was receiving placebo or corticosteroids. The Safety Monitor and the DCC will be informed immediately by the filing of a SAE report.

- In this setting, if the subject had been receiving corticosteroids, the tapering protocol will use a stress dose of hydrocortisone (50-62.5 mg/m2/24h) for 2-3 days, then physiologic replacement (20-25 mg/m2/24h) for 7 days, then half of the replacement dose for 7 days. The use of hydrocortisone, instead of prednisolone or methylprednisolone in the setting of infection, will minimize additional immunosuppression that would result from the glucocorticoid action of prednisolone during the taper schedule.

- Alternatively, replacement doses may be in the form of prednisolone (using the doses outlined for weeks 2-8 of Table 2), if the subject tolerates oral/enteric feedings.

When the steroid/placebo is discontinued, Ranitidine (Zantac®) will also need to be discontinued.

After the taper is completed, subjects may have some degree of adrenal suppression in the first year after the end of the steroid taper (although very unlikely). Therefore, stress doses of hydrocortisone may also be used during the first year after the steroid taper in any subject that may show signs of adrenal insufficiency during a severe infectious illness or a significant stress event (such as surgery).

The study code may only be broken to reveal if the subject was receiving placebo or corticosteroids if the physician treating the subject determines that knowing the information is necessary to implement his (or her) treatment plan. The Medical Safety Monitor and the DCC will be informed immediately by the filling of a SAE report.

4.5.3 Restarting Study Drug Related to Complication

When resumption of the study medication is not contraindicated by the type of complication, the study medication can be withheld when clinically indicated for up to 72 hours and then restarted. The investigator should file a protocol deviation (Form 40) when this occurs and the CRC should indicate this on the study medication CRF and on the website.

4.6 Steroid Pulses

Some investigators have used pulses of corticosteroids when there is delay or cessation of bile flow or cholangitis after portoenterostomy. Although there is no scientific evidence that this is an effective treatment, it is part of the clinical care sometimes provided by those investigators. The DSMB at its meeting on June 30, 2005, strongly recommended that steroid pulses not be used during this trial since its use may confound the results of the trial. The investigators and surgeons have agreed that there is no scientific evidence for its efficacy and therefore accept the recommendation of the DSMB. Therefore, the use of a steroid pulse during this trial will be treated as a protocol violation. If your study site chooses to use steroid pulsing, please complete a protocol deviation (Form 40) and send to the DCC.

In spite of agreement with the recommendation, it is recognized that protocol violations may occur. Since the size of the steroid pulse is also not standardized and in order to avoid providing too much steroids to subjects should an investigator choose to give a steroid pulse, the following policy will be adhered to:

- Irrespective of blinded randomization to treatment or non-treatment groups, if the attending physician chooses to use pulse steroids, the randomization code will not be broken.
- The dosage protocol for IV methyl prednisilone (Solumedrol) given as a single daily IV dose in the morning (with or without antibiotics as necessary) is as follows:
  - 5 mg/kg dose on day 1
  - 2.5 mg/kg dose on day 2
  - 1.0 mg/kg dose on day 3
  - 0.5 mg/kg dose on day 4 then stop.
- Document the use of steroid pulsing on Form S13B Steroid/Placebo and send to the DCC. Additionally, complete Form 40 Protocol Deviation any time a steroid pulse is used.

This is not meant to encourage steroid pulsing. However, when a steroid pulse is given, it will be given at the dose described in this policy in order to avoid an excessive dose of steroids being given to infants randomized to corticosteroids and, therefore, to eliminate the need to unmask the treatment prior to the administration of the steroid pulse.

4.7 Tracking Study Medication Use

- **Study Reduction Log (web-entry):** This web version log is used to provide a current summary of the subject's study medication status (web version only, there is no paper version to complete). At discharge, it is assumed that the subject is receiving all medications. This log should be updated when there is a change in any medications (stoppage, restart or reductions, increases that is not per protocol). This log may be updated at any time.

4.8 Administration Instructions for Study Medications

4.8.1 Administration Instructions for Steroid/Placebo

4.8.1.1 Schedule of Dosing

Study medication for this protocol includes methylprednisolone 40mg vials, Orapred® 15mg/5ml liquid and placebo liquid to match Orapred®. Methylprednisolone and Orapred® will be ordered through CCHMC wholesalers. Placebo liquid will be prepared by CCHMC IDS.

Table 3: Schedule and Dosing of Corticosteroids or Placebo following Portoenterostomy.

Day/Week of Dosing	Corticosteroids[1]	Placebo

Days 1-7 days 1-3 days 4-7	Methylprednisolone, IV – 4 mg/kg/day, divided BID Prednisolone, PO – 4 mg/kg/day, divided BID	IV – Normal saline (same volume, BID) PO – Placebo (same volume, BID)
Week 2	4 mg/kg/day, divided BID	PO same volume BID
Week 3	2 mg/kg/day, divided BID	PO same volume BID
Week 4	2 mg/kg/day, divided BID	PO same volume BID
Week 5	1 mg/kg/day, once a day	PO once a day
Week 6	1 mg/kg/day, once a day	PO once a day
Week 7	0.8 mg/kg/day, once a day	PO once a day
Week 8	0.6 mg/kg/day, once a day	PO once a day
Week 9	0.4 mg/kg/day, once a day	PO once a day
Week 10	0.2 mg/kg/day, once a day	PO once a day
Week 11	0.1 mg/kg/day, once a day	PO once a day
Week 12-	0.1 mg/kg/every other day	PO every other day
Week 14	Stop	Stop

[1]Initial dosage will be based on subject's weight. Subsequent doses will be adjusted based on subject's weight measured monthly at each scheduled outpatient visit.
Abbreviations: BID = Twice daily; IV = Intravenous; PO = Orally.

4.8.1.2 Guidelines for Giving a Second Dose if Child Spits Ups/Vomits First Dose

In the event that a subject spits up/vomits after being given a dose of the study drug/placebo, the subject's parent(s) or legal guardian(s) should be instructed to re-dose the study medication/ placebo using the guideline in Table 4.

Table 4: Re-dosing Following Spit Up/Vomiting of First Dose

Time Elapsed from Dosing Study Medication/ Placebo	Volume to Re-dose
0 to 30 minutes	Full dose
31 to 60 minutes	One-half dose
>60 minutes	Do not re-dose

Similar guidelines, without a time specification, are described in the protocol for re-dosing vitamins. The above time specification can also be applied to the re-dosing of vitamins.

4.8.1.3 Two-Week Drug Adjustment

The pre-surgical weight is the dosing weight. The weight should not be adjusted at the two-week visit, unless there is a clinical reason is indicated (a large drop in weight).

4.8.1.4 Instructions for the Family Administering Steroid/Placebo

1. Measure the liquid with the oral syringe provided. To use the syringe, first remove the white cap from the medicine bottle. Screw the provided blue cap onto the bottle.

Keep the bottle out of the reach of children. It will not be childproof with the blue cap. Unsnap the lid of the blue cap and place the tip of the syringe into the opening. Turn the bottle upside down and pull the plunger of the syringe back to allow medicine into the syringe. Draw up the prescribed dose of medicine. Turn bottle upright before removing the syringe. Replace the lid.

2. If your child vomits/spits up within 30 minutes of taking the medicine and empties the stomach, repeat the dose. If you are unsure, contact the study doctor.
3. Store medicine in the refrigerator.

4.8.2 Administration Instructions for AquADEK™ and Vitamin K (Mephyton®)

4.8.2.1 Schedule of Dosing

All cholestatic subjects with total bilirubin ≥1.5 mg/dL will receive:

- AquADEK™ vitamin drops: 2 ml orally per day up to 2 years of age.
- Vitamin K : 2.5 mg orally co-administered with AquADEK™ vitamin drops on Mondays, Wednesdays and Fridays.

AquADEK™ and Vitamin K may be stopped when the total bilirubin is <1.5 mg/dL. Serum vitamin levels and prothrombin time/International Normalized Ratio (INR) will be measured during the 1-month follow-up visit after portoenterostomy. When an abnormal value is obtained, the dosage of the specific vitamin will be augmented or reduced, as appropriate, and the level will be rechecked in 4 weeks (see Section 4N in protocol).

NOTE: If subject no longer meets criteria per protocol to continue this medication and the PI wants to continue for other medical reasons, the drug should no longer be provided by the study. The PI will need to write a prescription and the medication is to be paid by the subject's parent(s) or legal guardian(s) or third party payers.

4.8.2.2 Guidelines for Giving a Second Dose if Child Spits Up/Vomits First Dose

If the infant refuses the vitamin preparation or repeatedly spits it out, then the vitamins could be given in a small volume of formula (e.g. 15-30 ml) to help ensure full ingestion of the prescribed amount.

If the infant continues to refuse the vitamin preparation or repeatedly spits it out or vomits, the subject's parent(s) or legal guardian(s) will be asked to fill prescriptions for individual vitamins (A, D, E, and K; equivalent doses of AquADEK™); the individual vitamins are to be paid by them or by third party payers. The family will be instructed to not use any other vitamin preparations.

To reduce spitting up/vomiting, it is recommended that the dose may be given 1cc BID to help prevent spitting up/vomiting. Some sites will start the infant on 0.5cc four (4) times daily (QID) and then work up to 1cc. The dose should be given during feedings.

4.8.2.3 Accountability for Vitamins

Families will be asked to return bottles of the vitamin preparation and amount of solution remaining in the bottle will be recorded. In addition, the number of vitamin K tablets remaining will be recorded. A new supply of vitamins will be dispensed to provide enough supplementation until the next scheduled visit.

4.8.2.4 Instructions for the Family Administering AquADEK™ and Vitamin K

The families will be given a supply of AquADEK™ vitamins, including instructions on the daily dosing, advisements on volume of formula to give along with dosing, instruction for re-dosing (if dose is spit up/vomited), instructions for vitamin accountability and administering.

AquADEK™ Pediatric Drops

1. Measure the liquid with an oral syringe or medicine dropper.
2. If your child refuses the medicine or repeatedly spits it out, it can be mixed with a small amount of formula (15-30ml).
3. Store medicine in a closed container at room temperature.

Mephyton® tablets (phytonadione, vitamin K)

1. Cut tablet in half along score on tablet. Crush one half of the tablet and mix it with AquADEK™ vitamins. The remaining half of the tablet can be saved for the next dose.
2. Store medicine in a closed container at room temperature.

4.8.3 Administration Instructions for Ursodeoxycholic Acid (Urso 250® or Actigall®)

4.8.3.1 Schedule of Dosing

Ursodeoxycholic acid (Urso 250® or Actigall®) is given at 20 mg/kg/day divided BID orally up to 2 years of age or until bilirubin is >15 mg/dL.

Ursodeoxycholic acid will be discontinued if serum total bilirubin is >15 mg/dL to avoid potential toxicity. If subject no longer meets criteria per protocol to continue this medication and the PI wants to continue for other medical reasons, the drug should no longer be provided by the study. The PI will need to write a prescription and the

medication is to be paid by the subject's parent(s) or legal guardian(s) or third party payers.

4.8.3.2 Instructions for the Family Administering Ursodeoxycholic Acid (Urso 250® or Actigall®)

1. Shake the bottle well.
2. Measure the liquid with an oral syringe or medicine dropper.
3. Store medicine in a closed container at room temperature.

4.8.4 Administration Instructions for Trimethoprim-Sulfamethoxazole (TMP-SMZ) (Bactrim)

4.8.4.1 Schedule of Dosing

All subjects will receive antibiotics via IV for at least 2 days postoperative or until they are able to tolerate oral/enteric feedings. IV antibiotics are routinely used postoperatively at ChiLDREN study sites as prophylaxis against ascending cholangitis. The choice of antibiotics will be according to the local standard of care. Once oral/enteric feedings are tolerated, oral TMP-SMZ (Bactrim) (4-5 mg TMP/kg/day) will be initiated and continued for 6 months.

In the event of the occurrence of an episode of cholangitis, despite antimicrobial prophylaxis, subjects will be treated with parenteral antibiotics according to the standard of care at the study site where the subject is enrolled. Thereafter, prophylaxis with oral TMP-SMZ (Bactrim) will be used for 6 months. In addition to serving as prophylaxis against ascending cholangitis for all subjects, this regimen will also provide prophylaxis for pneumocystis carinii pneumonia (PCP) in subjects receiving corticosteroids.

If a subject no longer meets criteria per protocol to continue this medication and the PI wants to continue for other medical reasons, the drug should no longer be provided by the study. The PI will need to write a prescription and the medication is to be paid by the subject's parent(s) or legal guardian(s) or third party payers.

4.8.4.2 Dose Adjustment

- **Decreased Renal Function:** If the subject has evidence of decreased renal function, as indicated by an elevated serum level of creatinine, we will adjust the dose of TMP-SMZ (Bactrim) for renal insufficiency. These adjustments are based on a normal serum creatinine of <0.6 mg/dL in the first year of life.

  For serum creatinine:

  - >1.0 to 1.5 mg/dL, the dose will be reduced by 25%.
  - >1.5 to 2.5 mg/dL, the dose will be reduced by 50%.

- >2.5 mg/dL, the subject will be withdrawn from the study.

- **TMZ/SMZ Hypersensitivity:** In the unlikely event that the subject develops a hypersensitivity reaction to TMP-SMZ (Bactrim), the medication will be discontinued promptly and oral neomycin (25/mg/kg twice a day orally) will be used for prophylaxis against ascending cholangitis.

  Because neomycin provides no prophylaxis against PCP, the subject will also undergo a blinded taper and discontinuation of the study drug/placebo as outlined in Section 4.F3 of the protocol. The cost of the neomycin should be covered by each study site's grant (subject cost).

4.8.4.3 Instructions for the Family Administering TMP-SMZ (Bactrim)

1. Shake the bottle well.
2. Measure the liquid with an oral syringe or medicine dropper.
3. Store medicine in a closed container at room temperature.

4.8.5 Administration Instructions for Ranitidine (Zantac®)

4.8.5.1 Schedule of Dosing

Postoperatively, subjects will receive IV medication to suppress gastric acid production (H2 blocker or proton pump inhibitor, according to the local standard of care) until they resume oral/enteric feedings. Once they resume oral/enteric feedings, they will receive 12.5 mg BID oral ranitidine (Zantac®) (2-6 mg/kg/day, see Section 4.M.7 of protocol) while receiving the steroid/placebo; ranitidine (Zantac®) is approved by the FDA for use in children (1 month-16 years of age).

Because of the association between corticosteroid use and gastritis/peptic ulcer, all subjects will receive 12.5 mg orally BID (2-6 mg/kg/day) throughout the duration of the administration of study drug/placebo. Monthly supplies of ranitidine (Zantac®) will be dispensed by the research pharmacist to the subject's parent(s) or legal guardian(s).

If subject no longer meets criteria per protocol to continue this medication and the PI wants to continue for other medical reasons, the drug should no longer be provided by the study. The PI will need to write a prescription and the medication is to be paid by the subject's parent(s) or legal guardian(s) or third party payers.

4.8.5.2 Instructions for the Family Administering Ranitidine (Zantac®)

1. Dissolve one (1) tablet in 5 ml (1 teaspoonful) of water. Wait until the tablet is completely dissolved before giving the solution. Measure the liquid with an oral syringe or medicine dropper. Give 2.5ml (1/2 teaspoonful) of the liquid. Do <u>not</u> save any unused liquid.

2. Store medicine in original foil packaging at room temperature.

4.8.6 Administration Instructions for Immunizations

4.8.6.1 Schedule of Dosing

Subjects will receive all routine childhood vaccines according to the schedule recommended by the American Academy of Pediatrics (AAP), with the exception of up to a 4-week delay of vaccines that would have been given during the first 4 weeks of the study drug/placebo. Vaccinations will be administered by the subject's primary care provider. See details for immunizations and vaccine titers in 18-month follow-up visit descriptions.

4.9 Transferring START Subjects from One Clinical Site to Another

4.9.1 Subjects Taking Steroid/Placebo

4.9.1.1 Tasks: 'From'-Site (study site from which subject is transferring from)

1. Send email to: 'To'-Site CRC and Central Pharmacist
   - Provide subject's current ID number, randomization number, randomization date, and diagnosis and surgery dates.
   - Request new subject ID from the 'To'-Site CRC.

2. Form S35 Final Status completion
   - Question B1: Answer = 'No'.
   - Question B2: Answer = 'Transferred'. Enter the 'To'-Site subject ID as the 'Transferred to subject id'.
   - Question B3: Indicate the reason for the transfer and the date of transfer.

3. Form 35 Final Status completion
   - Question B1: Answer = 'Transferred'. Enter the new subject ID at the 'To'-Site as the 'Transferred to subject id'.
   - Question B2: Indicate the reason for the transfer and the date of transfer.
   - All other fields can be left blank.

4. Web Schedule Page update
   - Change the status from 'Active' to 'Transfer'. Leave 'Transferred from Subject ID' blank.
   - Ensure the subject has all drug needed to carry over to next scheduled visit date at the 'To'-Site.

4.9.1.2 Tasks: 'To'-Site (study site to where subject is transferring to)

1. Send email to: 'From'-Site CRC and Central Pharmacist
   - Provide the new subject ID number that will be used at the new site.
   - Inform Central Pharmacist the date on which drug will be needed (i.e., next scheduled visit date).
   - Obtain subject ID number that has been used at the 'From'-Site, as well as, randomization number, randomization date, and diagnosis and surgery dates, from the 'From'-Site CRC.

2. Enrollment at 'To'-Site
   - Enroll the subject as you would any other, using the next sequential subject ID number and binder that are available.
   - Complete Web Form 02A Subject Demographics.

3. Web Schedule update
   - Enter the randomization date and number used at the 'From'-Site and your own PROBE and START consent dates.
   - Indicate the status is "Transfer," and enter 'From'-Site subject ID as the 'Transferred from Subject ID'.
   - Enter the diagnosis and surgery dates from the 'From'-Site.

4.9.1.3 Tasks: Central Pharmacy

1. Determine whether the subject is on steroid or placebo. Based on the randomization number, prepare a new drug kit using the same randomization number, and send to 'To'-Site CRC by date requested.

4.9.2 Subjects Done Taking Steroid/Placebo

4.9.2.1 Tasks: 'From'-Site (study site from which subject is transferring from)

1. Send email to 'To'-Site CRC
   - Provide subject's current ID number, randomization number, randomization date, and diagnosis and surgery dates.
   - Request new subject ID from the 'To'-Site CRC.

2. Form S35 Final Status completion:
   - Question B1: Answer = 'No'.
   - Question B2: Answer = 'Transferred'. Enter the 'To'-Site subject ID as the 'Transferred to subject id'.
   - Question B3: Indicate the reason for the transfer and the date of transfer.

3. Form 35 Final Status completion

- Question B1: Answer = 'Transferred'. Enter the new subject ID at the 'To'-Site as the 'Transferred to subject id'.
- Question B2: Indicate the reason for the transfer and the date of transfer.
- All other fields can be left blank.

4. Web Schedule Page update
   - Change the status from 'Active' to 'Transfer'. Leave 'Transferred from subject ID' blank.

4.9.2.2 Tasks: 'To'-Site (study site to where subject is transferring to)

1. Send email to: 'From'-Site CRC
   - Provide the new subject ID number that will be used at the new site.
   - Obtain subject ID number that has been used at the 'From'-Site, as well as, randomization number, randomization date, and diagnosis and surgery dates, from the 'From'-Site CRC.

2. Enrollment at 'To'-Site:
   - Enroll the subject as you would any other, using the next sequential subject ID number and binder that are available.
   - Complete Web Form 02A Subject Demographics.

3. Web Schedule update
   - Enter the randomization date and number used at the 'From'-Site and your own PROBE and START consent dates.
   - Indicate the status is 'Transfer', and enter 'From'-Site subject ID as the 'Transferred from Subject ID'.
   - Enter the diagnosis and surgery dates from the 'From'-Site.

CHAPTER 5. SPECIMEN COLLECTION

5.1 Vitamin Levels Assessment

5.1.1 Schedule

Vitamin levels will be assessed while the subject is receiving vitamin supplementation or until the time of transplant:

- 1 month after entry into the study.
- 3- and 6-month follow-up visits.
- 12, 18, and 24 months of age.

If a subject no longer receives the vitamin supplementation because the total bilirubin concentration is <1.5 mg/dL, the vitamin concentrations will be checked at all the above times except at 18 months of age. Blood will be obtained at the study visits before the daily dose of vitamins is given.

The Clinical Research Coordinator (CRC) will call the family prior to the visit to remind them to not give the morning dose of vitamin supplements and that we would like to obtain blood when the infant has not had formula or food for approximately 4 hours.

5.1.2 Testing

The Pediatric CTRC Core Laboratory at The Children's Hospital in Denver will perform the vitamin testing, except for the Proteins Induced by Vitamin K Antagonism or Absence (PIVKA-II). The PIVKA-II sample will be held at the study site and then shipped to the repository at Fisher BioServices on a monthly basis, along with other specimens that are sent to Fisher BioServices.

The priorities for analysis of the vitamin and bile acid levels (if a specimen is insufficient in volume for all to be analyzed), unless otherwise specified by the study site or dictated by clinical care, will be the following order:

1. Vitamins A (retinol) and E (alpha tocopherol)
2. 25-hydroxy-Vitamin D
3. Total serum lipids
4. Retinol binding protein (RBP)
5. PIVKA
6. Total bile acids

5.1.3 Sample Size Requirements

The Pediatric CTRC Core Laboratory at The Children's Hospital in Denver requires serum volumes as follows to conduct specific vitamin tests:

• 500 µl of serum to assay Retinol, Alpha and Gamma Tocopherol, and Total Lipids.
• 300 µl of serum for Retinol Binding Protein (RBP).
• 200 µl of serum for 25OH Vitamin D and Total Bile Acids.

Fisher BioServices requires serum volumes as follows to conduct specific vitamin tests:

• 300 µl of serum for the PIVKA-II assay.

5.1.4 Specimen Labeling

- Prepare three (3) amber vials provided by the Data Coordinating Center (DCC). Label using manifest labels (Form 90). Write subject name, medical record number, and Date Of Birth (DOB) on label. Do **NOT** include study ID number or barcode on these vials. Use a Sharpie or other type of permanent non-smudge marker to write on label. (Securline® makes a marker Marker II/SuperFrost that works well). **Please write legibly.**

  NOTE: To ensure that labels remain attached to vial, label cryovials a few hours before they are to be placed in freezer. Wrapping scotch tape over labels before freezing helps to secure label on vial.

- Prepare one clear "repository" vial, provided by the DCC. Label with the 10th barcoded manifest labels (Form 51, label is pre-identified as "PIVKA"). Some Form 51's may not contain a pre-identified PIVKA label, if this is the case use the 10th label on this manifest anyway. Do **NOT** include any Protected Health Information (PHI) on this vial.

5.1.5 Specimen Collection and Processing

Collection: Draw 3.0cc of blood into a gold-top Serum Separator Tube (SST) vacutainer. Once drawn, cover the vacutainer with aluminum foil to protect it from light.

Centrifugation: Centrifuge the sample to obtain serum.

Aliquot: Aliquot plasma into labeled vials.

- 500 µl into the first amber vial.
- 300 µl into the second amber vial.
- 200 µl into the third amber vial.
- 300 µl into the clear vial.

Store filled cryovials in –70°C freezers.

5.1.6 Shipping Procedures

Amber Vials

Complete the shipping manifest form (Form 90). Use Sharpie or other type of permanent non-smug marker to write on manifest. (Securline® makes a marker Marker II/SuperFrost that works well). **Please write legibly.** You may also attach subject's clinical label to manifest if available.

Ship the three amber vials labeled with PHI only, on dry ice, to Denver using FedEx overnight, along with a copy of Form 90. Do **NOT** send the DCC a copy of Form 90.

NOTE: Shipping Supplies

- Study sites need to supply their own shipping boxes. Denver will return the shipping boxes to the CRC once specimens have been received. If you would like your shipper returned, include a pre-completed Fed-Ex or UPS shipping slip (including your study sites billing information) along with your specimen shipment. Denver will ship the box back to you.
- The DCC does not supply pre-paid Fed-Ex or UPS shipping slips for vitamin levels sent to Denver. Study sites must pay for shipping charges out of their study budgets.

The address of the repository in Denver is:
Pediatric GCRC Core Laboratory
Attn: Peggy Emmett
The Children's Hospital
13123 East 16th Avenue, Room A0922
Aurora, Colorado, 80045

Notify the laboratory by phone (720-777-8209) or fax (720-777-8100) a copy of the completed manifest (Form 90) when a shipment is sent, so the lab can anticipate its arrival. Email may also be sent to: corelab@tchden.org or Emmett.peggy@tchden.org to alert the lab that a specimen has been shipped. **Note:** These emails addresses may not be checked daily.

Overnight shipments should only be sent on Monday, Tuesday and Wednesday; DO NOT SHIP ON THURSDAY OR FRIDAY.

Clear Vial

Complete the shipping manifest form (Form 51). Ship the one clear vial labeled with barcode only, to Fisher BioServices, along with monthly batch shipment of other specimens to Fisher BioServices.

5.1.7 Results

The Denver lab will generate reports that are sent to each study site. Denver's goal is to have the results back to the PI within 7 days or receipt. RBP can take an extra few days. The Denver Lab will make every effort to include the RBP in the 7-day turn-around time. The lab will contact the study site when there is either a delay in getting the results or if any abnormal results are detected. If a problem occurs with the RBP, the other results will be sent without the RBP to the Principal Investigator (PI) as soon as completed. When the RBP is finished, these results will be sent separately.

5.2 Whole Blood for Genetics

Whole blood for genetics is collected as part of PROBE; refer to the PROBE MOO for specifics on collection.

NOTE: If a START subject is transplanted prior to their first birthday, blood for genetics should be collected after the transplant. This specimen can be collected as part of PROBE or START.

5.3 Antibody Titers

Subjects will receive all routine childhood vaccines according to the schedule recommended by the America Academy of Pediatrics (AAP), except that immunizations will not be given for the first 4 weeks after portoenterostomy (a period of time when the corticosteroid/placebo dose is 2-4 mg/kg/day). The normal immunization schedule will then be resumed, with immunizations to be given prior to one year of age being delayed by up to 4 weeks. If there is a need to catch-up with routine immunization schedule, it is anticipated that the catch-up schedule recommended by the Committee on Infectious Diseases of the AAP will be used by the primary care provider.

At the age of 18 months, if the subject has not been transplanted, 3 ml of blood will be obtained to measure serum antibody titers against individual vaccine antigens. These antibody titers will be done at the study sites local clinical laboratory and paid for out of the study sites study budget.

Results from the antibody titers will be recorded on Form S22V. If serum antibody titers do not achieve protective levels, the information will be provided to the primary care provider so that booster/re-immunization of appropriate antigen(s) is given. Absent titers will also be communicated to the primary care provider, who will treat with re-immunization as directed by the AAP guidelines for catch-up immunization.

CHAPTER 6. ADVERSE EVENT (AE) / SERIOUS ADVERSE EVENT (SAE) / REGULATORY BODIES REPORTING

6.1 Definitions

AE: An AE is any unfavorable, harmful or pathological change in a research subject as indicated by symptoms, psychological or physical signs and/or clinically significant laboratory abnormalities that occur in association with the study procedures. This definition includes intercurrent illness, injuries, exacerbation of pre-existing conditions. Stable pre-existing conditions and elective procedures to address such conditions are not AEs. A change in a laboratory variable is considered an AE, if it was considered by the PIs to be clinically significant (that is, if it institutes a diagnostic evaluation or indicates additional therapy is necessary).

SAE: A SAE is based on patient outcome that is associated with events that could threaten a patient's life or functioning.

A SAE is defined as any AE that results in any of the following:

- Death.
- Is life-threatening (subject was at risk of death as a result of the event; it does not refer to hypothetical risk of death if the event had been more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Expected AE: An Expected AE is any AE, the specificity and severity of which is consistent with the current standard of care, or is consistent with the risk information described in the informed consent document. The list of Expected AEs is compiled by the Steering Committee (SC) and is included in the protocol and in the informed consent documents.

Unexpected AE: An Unexpected AE is defined as any AE, the specificity and severity of which is not consistent with the current standard of care; or the specificity and severity of which is not consistent with the risk information described in the informed consent document or elsewhere in the current application.

Any expected or unexpected adverse event that also qualifies as a serious adverse event based on the criteria above is considered a serious adverse event by definition.

'Related to Study': The phrase 'related to study' implies causality or attribution to the study procedures. For purposes of defining as SAE, if a causal relationship cannot be ruled out, then an AE should be considered 'related to the study procedure(s)'. As noted above, it is very unlikely that any AEs will be attributable to this study.

Details and more information about AE/SAE's can be found in the study protocol.

6.2 Procedures for Reporting Serious Adverse Events (SAEs)

If a subject has been randomized into the START study (i.e. informed consent form signed), but has not yet received study treatment, the study sites must still report all SAEs.

6.2.1 Personnel Involved with SAEs

An investigator from the Data Coordinating Center (DCC) will serve as the Medical Safety Monitor. He (or she) will carry a pager so that all SAEs may be reported promptly. The Data and Safety Monitoring Board (DSMB) will review all AEs and SAEs during their regularly scheduled meetings, or on an expedited basis as determined by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Program Official, NIDDK Project Scientist and the DSMB, according to the DSMB Charter.

6.2.2 Contacts for Reporting of SAEs

Email all questions regarding SAEs to: children-SAE@umich.edu.

Primary contact:
James M Lopez, M.D.
Medical Safety Monitor
1500 E. Medical Center Dr.
MPB D5243, Box 0718
Ann Arbor, MI 48109-0759
Main Phone: (734) 936-7557
Office: (734) 763-9650
Pager: (800) 308-0933
141115
Fax: (734) 763-7359
Email: jamlopez@umich.edu

Alternate Contact:
Patricia R. Robuck, PhD, MPH
Clinical Trials Program
Div. of Digestive Diseases & Nut.
NIDDK
6707 Democracy Blvd., Rm 659
Phone: (301) 594-8879
Fax: (301) 480-8300
Email: pr132Q@nih.gov

Back-up Contact:
Project Manager
DCC
P: (734)615-9051
F: (734) 647)3711
children-pm@umich.edu

6.2.3 Automated SAE Notification System

All SAEs require expedited event notification within 24 hours of occurrence or notification to the study site.

1. Expedited event notification is completed through web-entry of the Adverse Event form (Form 45).

2. Submission of Form 45 triggers an email message to:

- Medical Safety Monitor to check the website for the report: no personal identifying or medical information is contained in the email message.
- NIDDK Program Official (Ed Doo)
- NIDDK Project Scientist (Pat Robuck)
- DCC Principal Investigator (PI)
- Project Manager (PM)

3. Web notification by the Clinical Research Coordinator (CRC) will generate an email message informing the CRC and PI that the notification has been received.

4. The Medical Safety Monitor reviews the information submitted on Form 45. If additional information is required to draft a preliminary report of the SAE, the CRC, at the study site with an SAE, will be contacted via an automated email message from the Medical Safety Monitor. Questions will be posted at the bottom of the web page in the "Comments" section.

   To access Form 45 on the web, click on "Access Data" for START from the study table. Under "Choose a Subject", highlight specific patient for which query was sent; click on "SAE Summaries". On table of all subjects at a specific study site that have entered SAEs, find the subject and event number being queried on. Under "Status" on this table, the queried subject will read "Medical Monitor Query". Click "Edit", which will open the SAE report. Scroll down to the Query/Response section where comments from the Medical Monitor are displayed. Type a response below the queries and change the Report Status to "Site Response"; click "Save". The response will be sent to the Medical Safety Monitor. You will receive an e-mail that you have sent a response to this query.

   NOTE: This query and answer process may rotate back and forth between the Medical Safety Monitor and the CRC multiple times.

5. Any changes made to Form 45 will generate an updated report through the same process that the original SAE report was entered. Updates continue to be made until an outcome and end date for the event is known or if the study participation ends.

6. Once resolved, a final SAE report is generated by the Medical Safety Monitor. The study site is notified via email from the DCC that the final report is posted to the website.

7. The study site prints out the final SAE report, has the PI sign the final report, and files the signed report in the subject's binder.

8. All SAE reports will be reviewed by the DSMB cumulatively at each DSMB meeting, and SAEs that have occurred since the previous meeting will be discussed individually by the DSMB. The NIDDK Program Official and NIDDK Project Scientist, with input from the Chair of the DSMB, will decide if any individual SAE warrants notification to the Food and Drug Administration (FDA) and to the Institutional Review Board's (IRB's) of all participating ChiLDREN study sites.

6.2.4 Reporting to the Food and Drug Administration (FDA)

The NIDDK Program Official, NIDDK Project Scientist and the Chair of the DSMB decide if any individual SAE warrants notification to the IRBs of all participating ChiLDREN study sites.

The Medical Safety Monitor will submit an expedited report to the FDA when the SAE is unexpected and may be related (even remotely to the study drug). Reporting to the FDA is under a strict timeline (as soon as possible, but no more than 7 days) when the SAE is unexpected, related to the medication and results in death.

6.2.5 Reporting to the Local Institutional Review Board (IRB)

The study site at which the SAE occurred is responsible for reporting of the SAE to their respective IRB according to the local guidelines at the study site. All SAE final reports will be available on the ChiLDREN website for those study sites that need to submit SAEs that occur at other study sites.

6.2.6 Forms Completion for SAEs

6.2.6.1 Form 45 Adverse Event (web-entry)

Form 45 Adverse Event is used to report SAEs. All SAEs (new or updated) reported on Form 45 must be web-entered at the study site.

- **Specific Form 45 Questions**

A4. Form 45 has a check box to indicate if this report is "Initial" (new SAE/AE) or an "Update" (used to update the data from a previously submitted event). Both are completed by web entry from the study site.

B1. Although Form 45 has a check box option to identify if the event is an SAE (Yes/No), this form should <u>only</u> be used for reporting SAEs. There is a separate mechanism for reporting AEs.

- **Initial Event Numbers:** During the course of the study, some subjects may experience several SAEs that are reported on Form 45. In order to differentiate between events each SAE will be assigned an event number. The event number will automatically be issued when a new SAE is entered on the ChiLDREN's website.

For example, the first SAE experienced by a subject would be event #01, the second would be event #02, the third would be event #03, etc… Each different event number represents a different SAE.

- **SAE Updates:** Once a SAE is entered into the database, the study site can update the original SAE as needed. Updates to an event are submitted to the DCC through web-entry of the SAE Form 45. An updated report is generated through the same process that the original SAE report was entered (use the same event number but a new report date).

  The system will automatically assign an update number to the original event number. When updating an SAE, the system will ask the investigator/CRC to select the original event number that the update is pertaining to and then will automatically apply the update number when any data is changed. When updating, document new and additional information obtained since the previous SAE form submission(s) regarding the same event (i.e., additional treatments, diagnosis, outcome, etc). Do not leave blank fields.

  If the subject is hospitalized; an update should be made if the subject's condition worsens or improves (e.g. transferred out of ICU, transferred to ICU, requires an operation, etc.)

- **Unresolved SAEs:** Unresolved SAEs should be updated weekly at the study site until the event is resolved and an end date for the event is known or study participation ends. The DCC PM and/or Medical Safety Monitor may send an email reminder to the study sites to request update of unresolved SAEs. All updates to unresolved SAEs go to the Medical Safety Monitor.

6.2.6.2 Form 45A SAE Supplemental Data

Form 45a is used to report supplemental data for any SAE that is classified as infectious.

Examples of an infectious SAE may include:

- Cholangitis
- Sepsis
- Viral infection
- Urinary Tract Infection (UTI)
- Upper Respiratory Infection (URI)
- Bacteremia, etc…

Form 45A is completed once Form 45 (original SAE and associated updates) are finalized. Reminder emails from the DCC may be sent to the study site indicating that the form needs to be completed. Form 45A is located on the website study table under the section "Other forms that may be necessary". It is a paper-based Case Report

Form (CRF). Therefore, the completed CRF should be sent to the DCC along with other CRFs related to the subject.

6.3 Other Reporting Scenarios

6.3.1 Unexpected SAEs

Unexpected SAEs must be reported using Form 45. The Medical Safety Monitor will submit an expedited report to the FDA when appropriate. Reporting to the FDA will occur as soon as possible, but no more than 7 days when the SAE is unexpected, related to the medication and results in death.

6.3.2 Unexpected, Non-Serious AEs

Unexpected, non-serious AEs are reported to the DCC either by:

- Documentation on a follow-up CRF (see summary below).
- Unexpected Non-Serious AE Log.

  The Unexpected Non-Serious AE Log is a web-entry form for each subject that experiences an unexpected, non-serious AE that is not captured on any of the START CRFs. This log is a running (active) document and should be updated until the outcome of the event is resolved and there is an end date.

  - If updating a previously reported AE, indicate so in the appropriate column. Update this log at the end of each START visit.
  - If no changes or new events have occurred for a visit, check none in the appropriate column.
  - If at anytime the event progresses to a SAE, it must be reported to the Medical Safety Monitor using Form 45.

6.3.3 Expected AEs During Follow-Up Visits

The list of Expected AEs is compiled by the SC and is included in the protocol, the informed consent document and the CRFs (e.g. Form 25 (C-M) sentinel events. Form S20 (B-J) AE screening, etc). At each follow-up, visit the study site will report all expected AEs on the appropriate CRF. If the AE is expected and serious, it is considered a SAE and Form 45 must be completed.

6.3.4 SAEs After Transplant for START

The DSMB recommends **NOT** reporting AEs or SAEs during the post-transplant period due to the fact that most subjects will have numerous AEs and SAEs unrelated to biliary atresia. Therefore, no SAEs will be reported post-transplant and transplantation is not considered a SAE.

6.3.5 Reporting Summary

SAEs

- All SAEs require expedited event notification within 24 hours of occurrence or notification to the study site.
- Expedited event notification is completed through web entry of the form Adverse Event
- If an AE is classified as a SAE, report the event on the appropriate AE Screening forms (Forms S20 and S20 (B-J)) and file as a SAE (Form 45).

AEs

- If an event required a medical visit/appointment and does not meet the requirements of a SAE, report the event on the Medical History form (Form 24) and the appropriate Sentinel Event form (Form 25 (C-M)), if applicable. If the event is found during completion of the AE Screening assessment (Form S20), report the event on the corresponding AE Screening form (Forms S20 (B-J)).
- Any non-serious AE that requires an intervention (new medication, change in medication, additional procedure, etc.) should be reported. If the CRF (e.g. AE Screening Form S20 (B-J) or Sentinel Events form (Form 25 (C-M)), etc.), does not have an appropriate place to document a non-serious AE, enter the event in the Unexpected Non-Serious AE Log on the web.
- All reports on Forms 20, S20 (B-J), 24, 25, 26, 27 and the AE log will be classified by the DCC as AEs. Form 45 should not be completed, unless the AE is classified as a SAE.

6.4 Monitoring and Management of Specific Expected AEs

Several side effects of corticosteroids are anticipated in the subjects randomized to corticosteroid treatment. The following section outlines the plan for monitoring and management of these AEs.

This monitoring will be conducted after portoenterostomy, but before the first dose of study medication is given (to provide baseline data), at hospital discharge and at each scheduled follow-up visit. **If initial hospitalization is extended due to any of these AEs, report as a SAE on Form 45 Adverse Event.**

There are two potential sets of risks associated with this clinical trial.

1. Derivations from the time of blood draws and includes amount of blood, as well as pain, bruising, or superficial phlebitis.

2. Derivations from reported side effects of corticosteroids, which include hypertension, hyperglycemia, hypokalemia, impaired wound healing, gastrointestinal bleeding, pancreatitis, and irritability.

Despite these potential AEs, this clinical trial is justified by the devastating nature of biliary atresia on the well-being of affected children and on the progression to end-stage liver disease in most patients. In this context, corticosteroid treatment may result in improved bile flow, allow for better growth, and long-term survival with the native liver. To minimize potential AEs to subjects, the investigators will monitor closely for side effects in all subjects, and promptly adhere to the action plan outlined in the Data and Safety Monitoring Plan (DSMP) if side effects are identified.

6.4.1 Hypertension

6.4.1.1 Measuring Blood Pressure (BP)

A Doppler instrument will be used to measure BP. BP measurement should begin after 5 minutes of rest and when the infant is quiet. A bladder width measuring 6 cm (infant size) will be used. The infant will be supine with the right arm resting on a supportive surface at the heart level. Two (2) BP readings will be obtained and separated by 2 minutes. The readings will be averaged. If the first two readings differ by more than 5 mmHg, additional readings will be obtained and averaged.

6.4.1.2 Hypertension Prior to the First Dose of Steroid/Placebo

The PI should be contacted to see if it is acceptable to give the first dose of steroid/placebo if the subject's hypertension is:

- Significant (systolic Blood Pressure (BP) ≥112 mmHg), as measured during hospitalization at least two times.
- Determined to be related to post-operative pain.
- Within 24-48 hours post surgery.

The PI may elect to administer pain medication and recheck BP prior to the first dose of steroid/placebo.

6.4.1.3 Hypertension at Follow-Up Visits

1. If a significant hypertension (systolic BP ≥112 mmHg for infants <12 months of age) is measured at least two times and the subject is asymptomatic, a repeat BP will be obtained within 24-48 hours. Upon repeat systolic BP:
   - If the elevated BP is resolved, no intervention will be necessary.
   - If the repeat systolic BP is ≥112 mmHg and the subject is asymptomatic, the study medication dose-reduction protocol (Section 4.F2) will be followed and a third repeat BP will be obtained within 48 hours. In the interim, a mild AE will be reported on Form S20B Hypertension.

2. If the third repeat systolic BP remains ≥112 mmHg, but the subject remains asymptomatic, anti-hypertensive monotherapy will be initiated (see below).
   - If the hypertension persists beyond 48 hours, a second dose-reduction will be initiated and a second anti-hypertensive medication may be used (see below).
   - If hypertension does not resolve within 48 hours or if the subject develops symptoms due to hypertension (e.g.: severe irritability, seizure) or other life-threatening consequences, such as end-organ damage, drug or placebo will be tapered and discontinued (Section 4.F3 of protocol), the subject will be referred to an emergency department, and additional anti-hypertensive treatment will be initiated. This AE will be reported as a SAE (Form 45).

6.4.1.4 Summary of Hypertension Action Plan

- If systolic BP is >112 mmHg, repeat BP after 24 hours and then again at 48 hours.
- If medication was prescribed, document all data on appropriate CRFs.
- If/When the study medication was reduced or tapered related to this AE, record on the appropriate CRF. Record repeated BP values that show the result of the intervention.
- If the subject's last recorded BP is elevated (systolic BP ≥112 mmHg), a resolution of this complication must be documented in the CRF. If this is unknown, complete Form 40 Protocol Deviation. When the condition is known to have resolved, complete the date of resolution, source, and BP after resolution (if known).

6.4.1.5 Treatment Choices

For hypertension with BP ≥112 mmHg <u>without</u> symptoms:

- Hydrochlorothiazide: 2 mg/kg/day given once or twice a day.
- Amlodipine: 0.2-0.4 mg/kg/day given once or twice a day.
- Captopril: 0.3-1 mg/kg/day given twice a day.
- Other study site-specific treatment choice.

For hypertension with BP ≥112 mmHg <u>with</u> symptoms:

- Nifedipine: 0.25-0.5 mg/kg/ sublingual.
- Labetolol: 1-3 mg/kg/hour via intravenous (IV) administration.
- Other study site-specific treatment of choice.

6.4.2 Hyperglycemia

A random plasma glucose level will be obtained at the time of discharge and at follow-up visits.

6.4.2.1 Measuring Hyperglycemia

When it is difficult to obtain a venous blood draw, accu-check can be used as a screen for hyperglycemia. If it is significantly elevated, a blood glucose will need to be obtained.

6.4.2.2 Hyperglycemia Decision Tree

1. If the random plasma glucose level is ≥200 mg/dL, the subject will return within 24 hours for a repeat level. Upon the repeat glucose level:
   - Is ≥200 mg/dL, a moderate AE will be reported on Form S20C Hyperglycemia and the study medication dose-reduction protocol (Section 4.F2) will be followed if the subject is asymptomatic.
   - Is 150-200 mg/dL, treatment or observation will be directed by the local standard of care, including the option for study medication dose reduction (Section 4.F2 of protocol).

2. Persistent hyperglycemia >200 mg/dL, beyond 48 hours of dose reduction and associated with acidosis or change in mental status due to elevated serum osmolality, will be considered a SAE (Form 45); the drug or placebo will be tapered and discontinued (Section 4.F3 of protocol).

6.4.2.3 Summary of Hyperglycemia Action Plan

- If glucose level is >200 mg/dL, repeat level within 24 hours.
- When the study medication was reduced or tapered related to this episode, record in the CRF. In addition, record study medication tapering or reduction. Record repeated glucose values that show the result of the intervention.
- If the subject's last recorded glucose level is elevated (glucose ≥200 mg/dL), a resolution of this complication must be documented. If this is unknown, complete Form 40 Protocol Deviation. When the condition is known to have resolved, complete the date of resolution, source, and glucose level after resolution (if known).

6.4.3 Hypokalemia

A random serum potassium level will be obtained at the time of hospital discharge and at follow-up visits.

6.4.3.1 Hypokalemia Decision Tree

1. If the random potassium level is less than the lower limit of normal (LLN), but >3.0 mmol/L, a mild AE will be reported on Form S20D Hypokalemia. A new serum potassium level will be obtained in 48 hours.
   - If the repeat potassium level is between 2.5 mmol/L and 3.0 mmol/L, a moderate AE (Form S20D) will be reported and appropriate replacement therapy will be initiated. Repeat serum potassium levels will be obtained at 24 and 48 hours after start of replacement.

- If the potassium is <2.5 mmol/L, a SAE (Form 45) will be reported, replacement therapy will be given immediately; the study drug or placebo will be tapered and discontinued (Section 4.F3 protocol), unless another cause is identified as the cause for the hypokalemia (such as use of furosemide or another diuretic that may be used because of progression of liver disease and development of ascites).

2. If the repeat serum potassium levels, after replacement therapy, do not normalize and the subject is asymptomatic, increased replacement will be initiated and the subject will be monitored closely. The PI will have the option to initiate study medication dose reduction (Section 4.F2 of protocol).

6.4.3.2 Summary of Hypokalemia Action Plan

- If potassium level is <3.0 mmol/L, record the replacement therapy in the CRF. Repeat the potassium level after 24 hours and then again at 48 hours.
- If/When the study medication is reduced or tapered related to this episode, record in the appropriate CRF. In addition, record study medication tapering or reduction on CRF. Record repeated potassium values that show the result of the intervention.
- If the subject's last recorded potassium level is elevated (potassium <3.0 mmol/L), a resolution of this complication must be documented. If this is unknown, complete Form 40 Protocol Deviation. When the condition is known to have resolved, complete the date of resolution, source, and potassium level after resolution (if known).

6.4.4 Impaired Wound Healing

Wound healing will be assessed daily in the hospital after portoenterostomy by the clinical team. A formal evaluation by the PI and CRC will occur on the day of discharge and at weeks 2 and 4 after portoenterostomy.

6.4.4.1 Impaired Wound Healing Decision Tree

Impaired wound healing is defined as a situation in which any of the following conditions are met:

- Re-admission due to wound healing complications after discharge following portoenterostomy.
- Delay in discharge due to wound healing complications after portoenterostomy.
- Wound infection after portoenterostomy that requires specific treatment with antibiotics.
- Return to the operating room in less than 30 days for wound management.
- A late complication in wound healing following portoenterostomy, such as, ventral hernia, ascitic leak, etc…

Any of these AEs will be reported a SAE (Form 45) and on Form 20E Wound Healing. In the event of any SAE, drug or placebo will be tapered and discontinued (Protocol Section 4.F3). Care of the subject for impaired wound healing will be done according to local standard of care.

6.4.4.2 Summary of Impaired Wound Healing Action Plan

- If wound separation is >25% of wound length, record any fascial dehiscence.
- When the study medication was reduced or tapered related to this episode, record in the appropriate CRF. In addition, record study medication tapering or reductions.
- If repeat hospitalization or surgery is required, report as a SAE and complete Form 45.

6.4.5 Gastrointestinal (GI) Bleeding

If hematochezia, melena, hematemesis, or visible blood through nasogastric or gastrostomy tube is reported, an evaluation of GI bleeding will be performed (e.g., to rule out anal fissure, infectious colitis, allergic colitis).

6.4.5.1 GI Bleeding Decision Tree

- If the GI bleeding is not associated with a drop in hematocrit and no further evaluation is indicated, a mild AE will be reported on Form S20F GI Bleed.
- If the presence of hematemesis, hematochezia or melena is associated with a drop in hematocrit of >5%, a moderate AE will be reported on Form S20F and further evaluation will be considered as clinically indicated; the PI will have the option to initiate study medication dose reduction (Protocol Section 4.F2).
- If a packed red blood cell transfusion is required and/or endoscopic intervention (such as sclerotherapy) is necessary, it will be reported as a SAE (Form 45). The presence of a hemoglobin level <6.5 g/dL or systemic hypotension caused by acute gastrointestinal bleeding will also be reported as a SAE; the study drug or placebo will be tapered and discontinued (Section 4.F3).

6.4.5.2 Summary of GI Bleeding Action Plan

- If GI bleeding was reported for any visit, the CRC should complete event on AE Screening form (Form S20) and record all interventions. In addition, the study site will record repeated hemoglobin and hematocrit values that show the result of the intervention.

6.4.6 Pancreatitis

Because a single diagnostic test for pancreatitis is not available, a combination of tests and the best clinical judgment of the PI will be used when evaluating the subject for possible pancreatitis.

6.4.6.1 Pancreatitis Decision Tree

1. If there is new onset irritability presumed due to abdominal discomfort, progressive abdominal distension, inability to feed and/or vomiting, a serum lipase and/or pancreatic ultrasound will be ordered.
   - If serum lipase is elevated (3 times above the upper limit of normal (ULN)) or ultrasound findings of pancreatitis are present, it will be reported as a moderate AE on Form 20G Pancreatitis; the PI will have the option to initiate study medication dose reduction (Protocol Section 4.F2).

2. If the symptoms persist or require narcotic pain medication, or are associated with a pancreatic pseudocyst, hypocalcemia or anemia felt to be secondary to hemorrhagic pancreatitis, a SAE (Form 45) will be reported; drug or placebo will be tapered and discontinued (Protocol Section 4.F3).

6.4.6.2 Summary of Pancreatitis Action Plan

- If pancreatitis was diagnosed at any visit, record the serum lipase level and all interventions. When hypocalcemia or anemia occurred related to the pancreatitis, record lab values on the appropriate CRF. Record reduced or tapered study medications related to this episode.

6.4.7 Irritability

Severe irritability is defined as the presence of inconsolable and persistent crying without an apparent cause, which requires evaluation and confirmation by the primary care provider or a visit to an emergency department if the subject is being followed as an outpatient, or by the clinical inpatient team if the subject is in hospital at the time of the event.

6.4.7.1 Irritability Decision Tree

1. Development of severe irritability in the subject, without an obvious cause, will be considered a moderate AE and reported on Form S20H Irritability.

2. Following evaluation for irritability and if no obvious cause is identified, a 50% dose reduction of study drug or placebo (Protocol Section 4.F2) will be considered by the PI.
   - If the irritability resolves on this reduced dose, the duration of reduced dose will be the same as for the original dose, and the subject will continue to follow the remainder of the scheduled study drug/placebo regimen. The Medical Safety Monitor will monitor all decreases in dose by study site.

3. If severe irritability persists despite the decrease in dosage, the study drug/placebo will be reduced by an additional 50%.

- If severe irritability persists despite this new reduction in dosage, the subject will undergo the tapering protocol and discontinuation of the study drug/placebo (Section 4.F3 of the protocol).

6.4.8 Hypersensitivity Reaction to Trimethoprim-Sulfamethoxazole (TMP-SMZ) (Bactrim)

If the subject develops a hypersensitivity reaction to TMP-SMZ (Bactrim) manifested by a skin rash, the medication will be discontinued promptly and oral neomycin (25 mg/kg PO twice daily) will be used as prophylaxis against ascending cholangitis. The AE should be reported on Form 25M Other Sentinel Events.

Because neomycin provides no prophylaxis against PCP, the subject will also undergo a blinded taper. The study medication will be discontinued as outlined in (Section 4.F3 of the protocol) and the subject will continue to be followed per protocol even when off medication. The choice to discontinue the study drug/placebo is based on concerns of the risk of PCP in the immunocompromised infant without TMP-SMZ (Bactrim) prophylaxis.

6.4.9 Cataracts

Cataracts are a well-recognized complication of long-term corticosteroid therapy, and are related both to dosage and duration of therapy. Children appear to be particularly at risk for steroid-induced cataracts. Despite the relative short duration of corticosteroid treatment in this clinical trial, all subjects will undergo an ophthalmologic examination at 12 months of age to monitor for the development of corticosteroid-induced posterior subcapsular cataracts. The examination will be performed by a pediatric ophthalmologist.

The incidence of cataracts in corticosteroid treated-subjects and in placebo controls will be reported to the DSMB. If cataracts are identified, report the AE on Form S20J Cataracts.

6.4.10 Vitamin Toxicity

There is a potential risk of vitamin toxicity from supplementation. However, specific toxic concentrations of each of the fat-soluble vitamins are not available in the literature. Therefore, close monitoring of vitamin levels to confirm that they are not above the normal ranges reported by the laboratory is planned and outlined in section 4.N8 and 4.N9 of the protocol.

Fat-soluble vitamin status will be checked within 1 month after starting supplementation through routine testing. Whenever a vitamin dose adjustment is made, follow-up testing will be performed within 1 month. If there is a major or rapid change in the severity of cholestasis (e.g., rapidly decreasing levels of serum bilirubin), vitamin levels will be monitored more frequently.

6.4.11 Any Infectious Acute Illness

Parent(s) or legal guardian(s) and primary care providers of all enrolled subjects will be instructed to contact the CRC promptly at the time of any infectious acute illness that leads to:

- Visit to the primary care provider.
- Visit to an emergency department.
- Required hospitalization of the subject.

Any of these conditions is considered a SAE and is reported on Form 45 Adverse Event within 24 hrs.

- If a child is hospitalized because of a respiratory tract illness of unknown etiology, microbiology studies will be pursued according to the local standard of care.
- An additional nasal aspirate will be obtained for rapid screen for *B. pertussis*.
- If *S. pneumoniae* is isolated from a sterile body site (e.g. blood, cerebrospinal fluid) or lower respiratory tract by bronchial lavage, the isolate will be serotyped to determine if it is a vaccine-related strain.

These diagnostic studies will be performed, when possible, by the admitting hospital's clinical microbiology laboratory. Alternatively, samples may be performed by an outside laboratory, such as Quest Diagnostic Laboratories.

6.4.12 Development of Septicemia and Opportunistic Infections

Subjects will be monitored for the development of infections or serious opportunistic infections (bacterial, viral, fungal). Evaluation of the subject with a febrile illness will proceed as per the local standard of care by the treating physician. In the absence of an emergent life-threatening event, antimicrobials will be initiated accordingly. A decision to break the study medication code is less likely to be necessary in these circumstances and should only be made in conjunction with the PI or designee based on the clinical status of the subject.

In the setting of an opportunistic infection (microorganisms that are uncommon in a patient with biliary atresia and not age-appropriate; e.g. fungemia in the absence of other predisposing factors such as broad spectrum antibiotics, indwelling lines, etc) or if the infection is associated with hypotension, acidosis, or tissue necrosis, antibiotic therapy and complementary medical management will be pursued by the treating physician based on standard care.

A decision about tapering and/or breaking of the study code will follow the guidelines in section 12.4.15 (Life-Threatening Events). Form 45 Adverse Event will be used to report the SAE.

All events with bacteremia, fungemia, or other opportunistic infections will be reported as an AE.

6.4.13 Adrenal Insufficiency

6.4.13.1 Adrenal Insufficiency While the Subject is Receiving Study Drug/Placebo Prior to the First Dose of Steroid/Placebo

Subjects will have a potential risk of adrenal insufficiency if administration of corticosteroids is suddenly discontinued after 2 weeks of treatment and/or during a sudden serious illness or traumatic event. This potential AE will be discussed and reviewed with the subject's parent(s) or legal guardian(s) at enrollment and at discharge from the hospital.

In subjects needing discontinuation of study drug/placebo for medical reasons (such as in the setting of a SAE, stress steroid administration with or without breaking of the study blind – reviewed below) or exit from the trial due to the subject's parent(s) or legal guardian(s) request, a tapering and discontinuation protocol will be used to prevent/minimize occurrence of adrenal insufficiency.

6.4.13.2 Adrenal Insufficiency Following Taper

Although it is unlikely, some subjects may have a degree of adrenal suppression for the first year following steroid taper. Therefore, stress doses of hydrocortisone may also be used during the first year after steroid taper in any subject that may show signs of adrenal insufficiency during a severe infectious illness or a significant stress event (such as surgery). The study code may only be broken to reveal if the subject was receiving placebo or corticosteroids if the physician treating the subject determines that knowing the information is necessary to implement his (or her) treatment plan. The Medical Safety Monitor and the DCC will be informed immediately through completion of Form 45 Adverse Event (Form 45).

6.4.14 Failure to Thrive or Poor Weight Gain

If the subject fails to thrive and/or has poor weight gain and is hospitalized as a result, it is reported as a SAE (Form 45). Therefore, discharge can generally be considered the SAE end date. However, because the subject is usually discharged on nasal gavage tube feeding, the outcome may have the status of "recovering". The study sites do <u>not</u> have to update this SAE weekly with the DCC.

6.4.15 Life Threatening Events

In the event of a life-threatening complication (e.g. hypotensive shock, severe acidosis, life threatening GI bleed, life threatening infection), the subject will be managed by the treating physician according to the standard of care and reported as a SAE (Form 45).

6.4.15.1 Breaking the Study Blind

If, in the opinion of the treating physician, the clinical situation requires knowing immediately if the subject is receiving corticosteroid, or had recently received corticosteroid (i.e. specifically potential adrenal insufficiency requiring a decision regarding whether or not to proceed with stress steroid administration), then breaking the study blind in conjunction with the research pharmacist so that appropriate emergency treatment can be undertaken is acceptable. The research pharmacist will notify the PI or designee immediately. It is the responsibility of the PI to ensure that he (or she) or his (or her) designee is available at all times.

The Medical Safety Monitor and the DCC will be informed immediately by the completion of a SAE report by the study site. The protocol for stress steroids and subsequent tapering will be decided upon by the treating physician depending on duration, dose of steroids administered, and the clinical situation.

If time permits, discussion regarding the need to break the study assignment should be carried out with the Medical Safety Monitor, the overall Study PI, and/or the National Institutes of Health (NIH) Project Scientist.

- If possible, information regarding which arm of the study the subject was assigned to will not be shared with the PI or designee by the research pharmacist unless he (or she) is the primary physician caring for the subject.
- The study site team should not share details regarding the study drug assignment with other ChiLDREN investigators.

CHAPTER 7. PREGESTIMIL

7.1 Schedule of Supplementation

- When the total bilirubin is ≥1.5 mg/dL and the child is less than 12 months of age, Medium Chain Triglyceride (MCT)-containing formula (Pregestimil) or breast milk should be used, as long as the child's growth is "adequate". MCT-containing formula will be continued until 24 months of age if the total bilirubin is ≥1.5 mg/dL and the child is over 12 months of age.
- When the total bilirubin is <1.5 mg/dL, the child can be transitioned to standard infant formula (if <1 year of age) and whole milk (if ≥1 year of age).
- When growth is inadequate, measures will be taken for nutritional rehabilitation according to medical management used at each Childhood Liver Disease Research and Education Network (ChiLDREN) study site.

7.2 Receiving/Shipment Schedule

To receive a supply of Pregestimil, the study site should contact Rhonda Wood, 812-429-7716 or rhonda.wood@mjn.com. Shipments arrive in 5-10 working days.

Pregestimil is being supplied to all study sites at no charge; therefore Mead Johnson will not be utilizing purchase orders. Mead Johnson will include paperwork with each shipment that contains the person's name to which it should be delivered. Dr. Sokol has supplied Mead Johnson with these names and addresses.

For future shipments requested by study sites, notify study site receiving department that additional formula is expected in 5-10 working days from Mead Johnson.

7.3 Dispensing

When dispensing formula for the subject's parent(s) or legal guardian(s), the study site will need to document what is given to the subject on the Pregestimil Log (see Appendix **A**), including:

- Date dispensed.
- Subject ID.
- Number of cases dispensed.
- Lot number.
- Expiration date.

7.4 Sterility

The subject's parents or legal guardian(s) will require instruction on reconstitution of Pregestimil, only as much as is to be used at a specific time. The study site should inform the subject's parent(s) or legal guardian(s) using the Pregestimil to make each bottle fresh. Once the bottle is made, it should be kept refrigerated and discarded if not used within 24 hours of preparation.

7.5 Returning Formula to Mead Johnson

Mead Johnson arranges for pick-up of the Pregestimil from the study sites and return to Mead Johnson for destruction. This formula cannot be returned to inventory. Prior to requesting pick-up, please contact Dr. Sokol for guidance on appropriate use of the excess formula.

If the final result is for pick-up, return and destruction of the product, contact Rhonda Wood, 812-429-7716 or rhonda.wood@mjn.com.

7.6 Damaged or Expired Formula

If study sites receive damaged formula, notify Rhonda Wood, 812-429-7716 or rhonda.wood@mjn.com of the quantity required for replacement. The study site should dispose of the damaged product in a manner that prevents further human consumption.

In certain circumstances, the degree of damage may still permit for dispensing of the product at the study site. If the study site continues to receive damaged product, call Rhonda to discuss resolution of the issue with the shipping company.

Damaged or expired product can either be disposed of at the study site or returned to Mead Johnson.

- If destroying the formula onsite, each can should be opened and the contents discarded in such a manner as to prevent human consumption.
- If returning the formula to Mead Johnson for destruction, contact Rhonda Wood.

7.7 Contacts

For shipping/receiving issues contact:
Rhonda Wood
Mead Johnson Nutritionals
2400 West Lloyd Expressway
Evansville IN 47721-0001
Phone: (812) 429-7716
Email: rhonda.wood@mjn.com

For other issues contact:
Kimberly Merkel, RPh
Manager, Contracted Clinical Services
Mead Johnson Nutritionals
2400 West Lloyd Expressway
Evansville IN 47721-0001

Phone: (812) 429-7881
Fax: (812) 429-5925
Email: kim.merkel@bms.com

Appendix A: Pregestimil Log

STUDY SITE NUMBER: _____

A Randomized, Double-Blinded, Placebo-Controlled Trial of Corticosteroid Therapy Following Portoenterostomy in Infants with Biliary Atresia.

Date:	P004 Subject Number	# Cases Dispensed	Lot #	Expiration Date	Staff Intials