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.