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.