PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
BABY HUG FOLLOW-UP STUDY

MANUAL OF OPERATIONS

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Prepared by:
Clinical Trials & Surveys Corp.
Suite 250
10065 Red Run Blvd.
Owings Mills, Maryland 21117

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CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 OVERVIEW

The Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) was designed as a Phase III, two-year study treatment, double-blind, randomized placebo-controlled trial including 200 children at 14 clinical centers. The final child was randomized into the BABY HUG Treatment Study in September 2007. At the end of their child's two years of study treatment, all parents/guardians will decide whether their child is to be treated with open-label hydroxyurea (HU) therapy, without regard to and without knowledge of their child's randomized treatment assignment. When originally consenting to participation in BABY HUG, parents/guardians were told explicitly of the investigators' intention to request permission to follow their child for many years, to evaluate possible long-term effects of treatment.

The purpose of the BABY HUG Follow-up Study is to provide structured follow-up of the children enrolled in the BABY HUG Treatment Study, in order to characterize the long-term toxicities and unexpected risks (if any) associated with treatment with hydroxyurea at an early age. Ideally this unique group of children should be intensively followed for growth, development, and clinical status at least through puberty or early adulthood to document any alterations in the natural history of sickle cell disease (SCD) associated with early HU therapy. The BABY HUG Follow-up Study is the initial installment in that effort.

All parents/guardians of BABY HUG participants will be offered enrollment of their child into the BABY HUG Follow-up Study, regardless of their original randomized treatment assignment. All children enrolled will be followed to a common termination date of December 31, 2011 or longer as funding permits. This plan will provide two or more years of follow up after the cessation of the original randomized treatment for each child. Although all

parents/guardians will be offered treatment with open-label hydroxyurea for their child after completing the BABY HUG randomized trial, participation in the follow-up study will not be contingent upon their subsequent treatment choice.

In the BABY HUG Follow-up Study, parents/guardians will be asked to consent to periodic reporting of clinically obtained information on their child including growth parameters, blood test results, transcranial Doppler (TCD) or other clinically obtained routine studies, and details of sickle cell disease related hospitalizations and health events. Collection and ongoing evaluation of growth and clinical data are key to the determination of long-term effects of hydroxyurea. Blood cells, serum, and urine will be collected at follow-up study entry and on a second occasion four years later or at study exit (4 years/exit) whichever comes first. This will provide samples for surrogate markers of toxicity and clinical efficacy, such as measures of renal and spleen function and markers of DNA damage (see Appendix A of the protocol – Exhibit 1-1). The stored blood sample will be separated, aliquots made and stored for future studies. Surplus blood and serum samples will be de-identified and stored in an NHLBI-sponsored repository (BioLINCC) for future studies with links to the de-identified clinical database of the BABY HUG Treatment Study. We believe that essentially all BABY HUG families will agree to this “passive” follow-up plan.

In addition, parents/guardians will be invited to have their child participate in an optional “active” reassessment two years after his/her exit from the BABY HUG Treatment Study. At that time, age-appropriate neuropsychological testing, abdominal ultrasonography, radionuclide liver-spleen scan, and an additional limited centralized blood sample for fetal hemoglobin (see Appendix A of the protocol), will be done. There will also be an additional neuropsychology test at the four year visit (Vineland). These studies will allow simultaneous assessment of unexpected nephrotoxicity or splenic enlargement and possible prolonged protection from organ dysfunction. Data collected in this follow-up study will be descriptively analyzed according to the

original treatment assignment (HU versus placebo), as well as the subsequent independent decision by families concerning use of open-label HU in the follow-up period.

Data collected in the passive follow-up portion will determine whether early hydroxyurea treatment is associated with long-term toxicities and provide limited data regarding long-term efficacy. Data collected in the active follow-up portion will identify long-term effects on organ dysfunction, and determine if duration of treatment and age of initiation (early vs. late) effect hydroxyurea's efficacy and toxicity. Information obtained from this follow-up study is vitally important to understanding the risks and benefits of early treatment, and ultimately for creation of an optimal paradigm for hydroxyurea therapy in young children with sickle cell anemia.

EXHIBIT 1-1
APPENDIX A
Schedule and Volume of Blood and Urine Collection and Schedule of Special Studies
BABY HUG Follow-up Observational Study

Time Point	CLINICAL DATA REPORTS	Blood Sample Collection (All volumes in ml)						Other Tests						
		HbF (Core)		HJB (Core)	Pitted Cells (Core)	STORED BLOOD SAMPLE	VDJ	Cystatin C (ml) (Core)	Creatinine and BUN (core)	Liver Spleen Scan	Abdominal Ultrasound	Neuropsych (WPPSI)	Microalbumin/ Creatinine Ratio Urine (Core)	Vineland
CONSENT (end of randomized study)		**		**	**	5.0^	**	0.5	**	**	**	**	5.0	
+6 Months	**X**													
+12 Months	**X**													
+18 Months	**X**													
+24 MO (Active Follow-Up Only) -1 month/+2 months	**X (all)**	0.5		0.1	0.1			0.5	0.5	Y	Y	Y		
+30 MO	**X**													
+36 MO	**X**													
+48 MO -1 month/+2 months	**X**			0.1	0.1	5.0^	3.0	0.5	0,5				5.0	**Y (for active follow-up only)**
+60 MO	**X**													
+72 MO or Exit	**X**													

CBC with diff and reticulocyte count will be done at each clinic visit as a clinical parameter. All CBCs performed for medical management within two months after completion of the BABY HUG Treatment Study should be reviewed only by the PEP.

** Done on exit from BABY HUG Treatment Study

^ The stored blood sample will be collected, separated and aliquots made and stored for future study

The entry visit has a time window of 3 months from consent signing for those who exited the BABY HUG Study > 6 weeks before enrolling in BABY HUG Follow-up and a time window of 6 weeks for those subjects who are entering the BABY HUG Follow-up Study immediately following the BABY HUG Treatment Study.

The 24 month Active special studies visit has a time window of -1month/+2 months.

The 48 month visit has a time window of -1month/+2 months.

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CHAPTER 2

PATIENT RECRUITMENT, ELIGIBILITY, AND INFORMED CONSENT

2.1 RECRUITMENT

Only children who were randomized into the BABY HUG Treatment Study may be recruited for enrollment in the follow-up study. When a child was consented for screening in the BABY HUG Treatment Study, parents/guardians were made aware that the Investigators wished to maintain contact with enrolled children after the treatment study ended for inclusion in a follow-up study.

2.2 ELIGIBILITY

All children who completed at least 18 months of follow-up visits in the BABY HUG Treatment Study are eligible for the BABY HUG Follow-up Study. The 18 months of follow-up can include the time period during the FDA's clinical hold on the treatment study (March 23, 2006 through June 1, 2006). Exclusion and inclusion criteria have already been evaluated for these subjects in the BABY HUG Treatment Study, so explicit eligibility criteria evaluation is not required again. However, please note that a child on a chronic transfusion program or one who is a recipient of a bone marrow transplant is eligible for this study. This is contrary to the BABY HUG Treatment Study.

The child will be enrolled in the follow-up study when s/he is declared eligible by the Data Coordinating Center DCC. The DCC will declare a child eligible upon verification that s/he participated in the BABY HUG Treatment Study for at least 18 months.

2.3 INFORMED CONSENT

A new informed consent from parents/guardians will be required for participation. Consent will be requested during the child's 24-month (exit) studies in the BABY HUG Treatment Study. For eligible children who have already exited the treatment study prior to the start of the follow-up study, consent should be requested as soon as possible.

Individual Clinical Center consent forms will be prepared based on the model informed consent form in the protocol. The model consent form will be approved by the Project Officer of the National Heart, Lung, and Blood Institute (NHLBI) and the Observational Study Monitoring Board (OSMB) prior to its release to the Clinical Centers for submission to the local IRBs. Each final consent form will be reviewed by (DCC) staff and a member of the OSMB to ensure all required elements of the consent form have been addressed.

The Clinical Center Principal Investigator (PI) will offer participation to each eligible family in the BABY HUG Treatment Study. The family will be given adequate time and privacy to review the consent form. They will have the opportunity to have all of their questions and concerns addressed by the PI.

An ombudsman, required for the BABY HUG Treatment Study consent process, may be present but is <u>not</u> required. A copy of the signed consent form will be given to the parent/guardians and placed in the child's medical record. The original will be maintained in study files by the PI or designee.

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CHAPTER 3

CLINICAL CENTER PROCEDURES

3.1 SCHEDULING

3.1.1 General Principles for Scheduling "Active Group" Tests

- Blood draws should be spaced as necessary; a general guideline for research blood draws is no more than 3cc/kg/8 weeks. When possible, blood draws should be grouped around IV starts in order to minimize the number of times the child is subjected to needle insertion. Another reason to do this is that blood for pitted cell counts should be drawn at or close to the time the liver-spleen scan is performed. Blood will be drawn at entry and 48 months for all patients, and additionally at 24 months for the active patient group only.
- For maximum attention and cooperation, neuropsychological testing should be performed when the child is alert and not hungry or sleepy.
- Some of the special study tests for the active patient group may require 4-6 weeks advance scheduling in some institutions. Therefore, it will be important to plan ahead for patients who elect active follow-up.

3.1.2 Visit Schedule

3.1.2.1 All Patients

All patients will have a baseline visit at study entry and one at exit or 48 months, whichever is earlier. Any standard clinical visits in between this period will be captured in medical chart reviews at 6 month intervals for the first three years and annually thereafter. The clinically ordered TCD that is performed closest to the 24 month time point should be captured on a CD and shipped to Judy Luden at MUSC (see Section 6.4) (TCD Performance) in StudyCTMS. The results of this TCD should also be included on the relevant Data Abstraction

Form (Form 10) for this time point and the report faxed to the DCC along with Form 105. The Visit Schedule (Section 3.3.1) indicates the dates when the visits and abstractions are to be conducted for each patient.

3.1.2.1.1 Baseline

At study entry, all patients will have two blood specimens collected: a Cystatin C (0.5mL) specimen if a result was not obtained at BABY HUG Treatment Study exit and a specimen (5.0mL) for long-term storage in the repository. A urine specimen (5.0mL) will also be collected for the Microalbumin: Creatinine ratio. Patients will be asked about their medical history, and any adverse (clinical) events they have been experiencing. Height, weight and head circumference will be measured if it is the standard of care for the Clinical Center. The length of time from BABY HUG exit to BABY HUG Follow-up Study entry will not dictate the need for a repeat Cystatin C. If a Cystatin C result was obtained at the BABY HUG Treatment Study exit, this specimen does not need to be collected at BABY HUG Follow-up Study baseline. (If the result was not obtained at BABY HUG exit, collect a specimen at BABY HUG Follow-up Study entry.) Refer to Exhibit 1-1 for a complete listing of required blood draws and special studies.

The time windows for completing the baseline tests are as follows. Record the tests on Form 03 (Study Entry).

A) For patients who exited the BABY HUG Treatment Study > 6 weeks before enrolling in the BABY HUG Follow-up Study, the initial tests for the BABY HUG Follow-up Study must be completed within 3 months of signing consent.

B) For patients entering the BABY HUG Follow-up Study immediately following their exit from the BABY HUG study, the initial tests must be completed within 6 weeks of signing consent.

3.1.2.1.2 Medical Record Abstraction

Every 6 months for the first three years and annually thereafter, Clinical Centers will abstract information from patients' medical records and enter it through the StudyCTMS data entry system via a Form 10 (Clinical Data Report). Copies of imaging and neuropsychological (e.g., non-Protocol related WPPSI or Bayley) results will be faxed to the Data Coordinating Center (DCC) using Form 105 (Imaging and Neuropsychological Reports Transmittal List). All identifying information, e.g., patient name, address, phone, date of birth, and medical record number, must be de-identified before sending the results to the DCC. All follow-up and abstraction will end on December 31, 2011.

Following are the tests, events and reports to be abstracted every 6 months if available:

- Lab results*
- TCD
- MRI
- MRA
- CT
- EEG
- PFT
- Neuropsychological
- Hospitalizations
- Surgical Procedures
- Transfusion
- Physical Exam

*For subjects who have more than one chemistry or fetal hemoglobin test done in a six month period, record the result which was obtained closest to the end of the visit window on Form 10.

3.1.2.1.3 48 Month Visit

Because the BABY HUG Follow-up Study will end on December 31, 2011, the 48 month procedures should occur 48 months after the patient's exit date from the BABY HUG Treatment

Study or within 2 months of December 31, 2011, whichever occurs first. The following lab tests will be performed for this visit:

- Howell Jolly Bodies (HJB) by flow cytometry, 0.1mL blood
- Pitted cell count, 0.1mL blood
- Blood specimen for repository storage, 5.0mL blood
- VDJ, 3.0mL blood
- Cystatin C, 0.5mL blood
- HPLC creatinine 0.5mL blood
- Microalbumin: creatinine urine ratio , 5.0mL urine

Please see Chapter 4 for the specifics of collecting and shipping the blood and urine specimens and Chapter 5 for procedural instructions for Active Group tests.

3.1.2.2 Active Patients

3.1.2.2.1 24 Month Visit

Active patients are those who agree to one extra set of tests at 24 months and a Vineland behavioral questionnaire at 48 months. These patients can decline any specific test(s) they choose and still be considered active. However, the goal is that all tests will be performed. The 24 month visit entails the following lab and clinical tests:

- Blood specimens (HbF, HJB, Pitted cell count, cystatin C and HPLC creatinine)
- Liver-spleen scan
- Abdominal ultrasound
- Neuropsychological test: WPPSI

Please see Chapter 5 for procedural instructions for the last three tests and the Vineland.

3.2 FORMS

The following list delineates each form number and its name. More information can be found in the StudyCTMS User Instructions manual in the Documents page within StudyCTMS or in the BABY HUG Follow-up Study Forms and Q x Q binder. Note that all numerical data entered on forms must have leading zeros, if necessary.

Enrollment forms (all patients)

01 Enrollment
02 Patient Treatment Plan
03 Study Entry

Data forms (all patients)

10 Clinical Data Report
11 48-Month Or Exit Laboratory Tests
12 Exit Form
13 TCD Study Form

Active patient forms

20 24-Month Special Tests And Laboratory Tests
21 Liver-Spleen Scan Performance
23 Abdominal Sonogram (Ultrasound) Performance
24 WPPSI
25 SAE Form
26 Stem Cell Transplant
27 Vineland

Transmittal forms (all patients)

100 MCG Transmittal Form
101 St. Jude Transmittal Form
102 UTSW Transmittal Form
103 DCC Transmittal Form
104 MUSC TCD Transmittal Form
105 Imaging and Neuropsych Reports Transmittal

3.3 StudyCTMS REPORTS

Two StudyCTMS reports are available to assist each Clinical Center in scheduling patient visits and in completing forms. They are the Appointment Schedule report and the Delinquent Forms report.

3.3.1 Visit Schedule

Please see Exhibit 3-1 for a sample Visit Schedule report. The Visit Schedule indicates the time periods for medical abstraction, and when the other specimens should be collected. You will see that for each patient, the visit number, the window start date, ideal date and window end date are depicted. Additionally, the procedures to perform at each visit are noted.

The time clock for the Visit Schedule begins with the date the patient had their exit DTPA GFR procedure in the BABY HUG Treatment Study prior to May 29, 2009. If the exit DTPA GFR procedure was not done in the treatment study, then the Visit Schedule starts on the day after the child's last dose of study treatment as determined by the coordinator and communicated to the DCC, or for children who withdraw, on the date of withdrawal (the start date on BABY HUG Treatment Study Form 36 – End of Randomized Study Treatment).

If, for example, a parent/guardian signs the BABY HUG Follow-up Study consent form two years after exiting the BABY HUG Treatment Study, the patient is ready for his/her 24 month visit if he/she is an active patient in the follow-up study. Please call a coordinator at the DCC should you have questions as to which tests to run for a patient dependent upon their enrollment date in the BABY HUG Follow-up Study and exit from the BABY HUG Treatment Study. There can be crossovers such that baseline and later visit tests will need to be run at the same time.

3.3.2 Delinquent Forms

Please see Exhibit 3-2 for a sample Delinquent Forms report. This report indicates for a specific visit number and subject ID, the date each form (was) is done and whether it is late. This form will serve as a reminder to complete what is outstanding.

If a patient is not seen within his/her time window, the Clinical Center Coordinator will need to record a protocol deviation and report it to the DCC. Additionally, the Clinical Center Coordinator will need to call the BABY HUG Follow-up Study DCC Coordinator for a discussion

regarding what tests and procedures to perform in the new timeframe; this discussion will receive input from the Steering Committee.

3.4 ADVERSE EVENT MONITORING

3.4.1 Adverse Events

Adverse (clinical) events will be recorded via abstraction on Form 10 (Clinical Data Report).

3.4.2 Serious Adverse Events

3.4.2.1 Definition

A **Serious Adverse Event** (SAE) is any one of the following:

1. Death
2. Life-threatening event
3. Prolonged hospitalization (greater than 7 days)
4. Splenic sequestration crisis
5. Stroke, TIA
6. Acute chest syndrome
7. ICU admissions
8. Unexpected adverse event and related to HU

SAEs that are SCD-related have been added to the FDA-defined list. Item # 3 has been modified from the FDA definition because frequent hospitalizations occur as a consequence of having sickle cell anemia without being enrolled in a clinical trial.

3.4.2.2 Monitoring

Standard clinical trial prospective SAE reporting for the events listed in 3.4.2.1 will occur only during the <u>five</u> <u>days</u> following the 24-month assessments of active follow-up patients. These are the only SAEs that are to be reported during the follow-up study. The OSMB will perform a semi-annual systematic review to determine if one treatment group (or HU exposure type) has more reports of SAEs than the other treatment group (or HU exposure type). See Chapter 9, section 9.3 for more information.

3.4.2.3 Reporting SAEs

Record all SAEs (see section 3.4.2.2.) on Form 25 (SAE Form). The duration of an event includes both the beginning and ending day of the event.

An unexpected adverse event is an event not previously identified in nature, severity, or frequency in the risk information described in the Protocol, informed consent or listed in the current hydroxyurea product labeling.

Each BABY HUG Follow-up Study SAE must be reported on a U.S. FDA MedWatch Form 3500A. Detailed information on completion of MedWatch Forms and an electronic template of the form are available at:

http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf

- Submit the MedWatch form by fax or e-mail to the BABY HUG Follow-up Study DCC at: (fax) 443-524-2320 or e-mail: bfish@c-tasc.com
- Fax the MedWatch to the BABY HUG Follow-up Study DCC within 24 hours of the Clinical Center becoming aware of the event.

3.5 MAINTENANCE OF STUDY RECORDS

3.5.1 Patient Records

Study-related patient records must be kept in lockable cabinets or file drawers, preferably in the Study Coordinator's office. The study does not mandate a specific system of patient record filing. Thus, each Coordinator should develop a well-organized filing system that optimizes the ability to easily retrieve specific files.

The source documentation for the BABY HUG Follow-up Study is the patient's medical record, special test results with study forms (e.g. liver/spleen scans – Form 21, and abdominal sonograms – Form 23), lab result printouts and the neuropsychological test booklets.

3.5.2 Coordinator Files

Material contained in the patient files that are maintained by the Coordinator should include, but are not necessarily limited to the following:

- Signed original consent forms
- Signed original HIPAA forms (if not incorporated in to the consent form)
- Record of family honoraria
- Printouts of the entered study forms
- Copies of neuropsychological evaluations
- Current medical records or a system for reviewing computerized records must be in place
- Copies of specimen and film transmittal forms

3.5.3 Clinical Center Records

The Study Coordinator should also designate a bookshelf or desktop space to keep a collection of binders for study materials including:

- Protocol, with all amendments
- Manual of Operations
- Forms
- Form QxQs
- Address Directory
- Numbered Memos
- Steering Committee Minutes
- Correspondence
    - With other Coordinators
    - Coordinator Conference call minutes
    - With the Coordinating Center
- Specific Clinical Center requirements
    - IRB and other administrative materials and approved documents
    - Local consent form
    - FDA Form 1572 and respective CVs

- Financial Disclosures
- Certifications
- Local special study performance directions and notes (e.g. TCD)

3.6 TRANSFER OF PATIENTS

3.6.1 Notification of Transfer

If a patient moves from one BABY HUG Follow-up Study Clinical Center to another BABY HUG Follow-up Clinical Center, the Study Coordinator of the original Clinical Center will discuss the pending transfer with the patient. The Study Coordinator will contact the new Clinical Center and provide the patient with the contact information for the Study Coordinator at the new Clinical Center.

A memo and PART 1 of Form A: Notification of Patient Transfer (Exhibit 3-3) must be completed by the original Clinical Center's PI and sent to the PI of the new Clinical Center informing him/her of the potential transfer. This will serve as a formal notice to the new Clinical Center that a patient is transferring. The memo should include:

1. Approximate date the patient is scheduled to move
2. Date of the last clinic visit
3. The Visit Schedule
4. A medical summary and other pertinent source documents
5. Patient's new address, telephone number and other relevant contact information. The patient's family should also provide contact information for a relative not residing in their household.
6. Copies of relevant study records

The new Clinical Center's Study Coordinator should also receive a copy of this memo. The DCC should receive a faxed copy of Form A.

3.6.2 Release of Medical and Study Records

Once a Clinical Center becomes aware of a patient's intent to transfer to a new Clinical Center, they may request that the patient's family sign a medical records release form. The form must contain the name of the patient, the signature of the parent and the party to which the patient's medical information is to be released. The medical records, study documentation and labels must remain at the original Clinical Center until the patient's family completes a medical release form.

The PI at the original Clinical Center should forward the patient's medical records to the PI at the new Clinical Center after the medical release form is signed. A copy of the patient's consent form, medical records and medical record abstractions should be sent to the new Clinical Center as soon as possible, prior to the patient's first clinic visit at the new Clinical Center.

The originating Clinical Center will retain the patient's original BABY HUG Follow-up Study records and send the new Clinical Center copies of all documents on file. The Study Coordinator at the original Clinical Center should clear all edits prior to the transfer of the patient. The patient must retain the original BABY HUG Follow-up Study patient identification number throughout the course of the study, even though it was assigned at the original Clinical Center.

3.6.3 Consenting the Patient at the New Clinical Center

The new Clinical Center must re-consent the patient to the follow-up study using their locally approved IRB consent. The patient must be informed that being at the new Clinical Center may come with new regulations, possibly including different IRB regulations and different state regulations. The patient becomes the responsibility of the new Clinical Center only after the informed consent for the new Clinical Center is signed.

3.7 CAPITATION REPORT

The Capitation Report is the billing statement for each Clinical Center, which tallies, for example, the number of medical abstraction forms completed, such that payment can be released to each Clinical Center. The Capitation Report will be sent from the DCC to the Clinical Centers quarterly (March, June, September, December). The PI will need to verify the information and sign the report. Each Clinical Center will need to send their signed Capitation Report to NHLBI (the direct payor) with an invoice from their business office.

EXHIBIT 3-1
VISIT SCHEDULE

Visit Schedule

Baby hug Follow-up Study
April 11, 2011

Clinical Center: 01 **Childrens National Medical Center**
Subject: 0107

Visit	Acceptable Start Date	Expected Start Date	Target/Scheduled Date*	Expected End Date	Acceptable End Date	Form #	Work Expected at Each Visit Form Name
A06	Aug-23-2007	Aug-23-2007	Feb-23-2008	Feb-22-2008	Feb-22-2008	010	CLINICAL DATA REPORT
A12	Feb-23-2008	Feb-23-2008	Aug-23-2008	Aug-22-2008	Aug-22-2008	010	CLINICAL DATA REPORT
A18	Aug-23-2008	Aug-23-2008	Feb-23-2009	Feb-22-2009	Feb-22-2009	010	CLINICAL DATA REPORT
000			May-05-2009	Aug-05-2009	Aug-05-2009	001	ENROLLMENT
						002	PATIENT TREATMENT PLAN
						003	STUDY ENTRY
24M	Jul-23-2009	Jul-23-2009	Aug-23-2009	Oct-23-2009	Oct-23-2009	020	24_MONTH SPECIAL TESTS AND LABORATORY TESTS (Active Patients Only)
						021	LIVER-SPLEEN SCAN PERFORMANCE
						023	ABDOMINAL SONOGRAM (ULTRASOUND) PERFORMANCE
						024	WPPSI FORM
						025	SERIOUS ADVERSE EVENT (ACTIVE GROUP ONLY)
A24	Feb-23-2009	Feb-23-2009	Aug-23-2009	Aug-22-2009	Aug-22-2009	010	CLINICAL DATA REPORT
						013	24 MONTH TRANSCRANIAL (TCD) EXAM
A30	Aug-23-2009	Aug-23-2009	Feb-23-2010	Feb-22-2010	Feb-22-2010	010	CLINICAL DATA REPORT
A36	Feb-23-2010	Feb-23-2010	Aug-23-2010	Aug-22-2010	Aug-22-2010	010	CLINICAL DATA REPORT
48M	Jul-23-2011	Jul-23-2011	Aug-23-2011	Oct-23-2011	Oct-23-2011	011	48-MONTH OR EXIT LABORATORY TESTS
						027	VINELAND SUMMARY
A48	Aug-23-2010	Aug-23-2010	Aug-23-2011	Aug-22-2011	Aug-22-2011	010	CLINICAL DATA REPORT
A60	Aug-23-2011	Aug-23-2011	Jan-01-2012	Dec-31-2011	Dec-31-2011	010	CLINICAL DATA REPORT

* Displayed in **BOLD** for scheduled dates

EXHIBIT 3-2
DELINQUENT FORMS REPORT

Subject 1008

Visit Nbr A06

Form Id	Due Date
010	MAY-30-2007
010	MAY-26-2007

Visit Nbr A12

Form Id	Due Date
010	NOV-26-2007
010	NOV-22-2007

Visit Nbr A18

Form Id	Due Date
010	MAY-24-2008
010	MAY-20-2008

Visit Nbr A24

Form Id	Due Date
010	NOV-16-2008

Visit Nbr A30

Form Id	Due Date
010	MAY-19-2009
010	MAY-15-2009

Subject Id 0102

Visit Nbr	Form Id	Due Date
001	001	JAN-02-2003
001	002	JAN-02-2003
001	003	JAN-02-2003

Subject Id 0103

Visit Nbr	Form Id	Due Date
001	001	MAR-01-2008
001	002	MAR-01-2008
001	003	MAR-01-2008

Subject Id 0104

Visit Nbr	Form Id	Due Date
001	001	JAN-02-2006
001	002	JAN-02-2006
001	003	JAN-02-2006

Subject Id 0105

Visit Nbr	Form Id	Due Date
001	001	AUG-17-2007
001	002	AUG-17-2007
001	003	AUG-17-2007

Subject Id 0108

EXHIBIT 3-3

BABY HUG FOLLOW-UP STUDY
NOTIFICATION OF TRANSFER PATIENT

BABY HUG Follow-up Study
Form A Rev. 9-30-08

PART I: FOR ORIGINAL CLINICAL CENTER COMPLETION

1. Patient ID: ___ ___ ___ ___

2. Date Form Initiated: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

3. Original Clinical Center: ___ ___

New Clinical Center: ___ ___

4. Anticipated Date of Last Clinic Visit at Original Center: __ __ __ - __ __ - __ __ __ __
Month Day Year

5. Anticipated Date of Transfer: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

6. Signature of Principal Investigator: _____

7. Is this transfer
Permanent ……..(1)
Temporary ……..(2)

PART II: FOR NEW CLINICAL CENTER COMPLETION

1. Date Consent Form Signed: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

2. Date First Clinic Visit Completed: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

3. Signature of Principal Investigator: _____

PART III: FOR DCC COMPLETION

1. Date patient transferred: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

CHAPTER 4

COLLECTION AND SHIPMENT OF SPECIMENS FOR CENTRAL LABORATORIES

4.1 OVERVIEW

The purpose of this chapter is to provide guidelines for the collection, preparation and shipment of blood and urine specimens to the BABY HUG Follow-up Study Core Laboratories. Table 4-1 summarizes the required Core Laboratory specimens. It should be noted that all specimens that will be shipped to the Core Laboratories must be shipped Monday through Thursday only. Core Laboratories cannot process specimens over the weekend.

TABLE 4-1

Summary of Core Laboratory Specimens

Specimen	Amount	Collection tube type	Frequency
Urine for Microalbumin: Creatinine	5 mL	Cryovial	Entry, 48 months
Stored Blood Sample	5 mL	EDTA lavender top	Entry, 48 months
Cystatin C	0.5 mL	Red top	Entry*, 24 months**, 48 months
HbF	0.5 mL	EDTA lavender top	24 months**
Howell Jolly Bodies	0.1 mL	EDTA lavender top	24 months**, 48 months
Pitted Cells	0.1 mL	EDTA lavender top w/gluteraldehyde	24 months**, 48 months
HPLC Creatinine	0.5 mL	Red top	24 months**, 48 months
VDJ	3.0 mL	EDTA lavender top	48 months

*Cystatin C should only be collected at entry if a specimen was not obtained upon exit of the BABY HUG Treatment Study. Coordinator should contact the DCC to verify whether or not Cystatin C should be collected at entry.
**Specimen should only be collected at 24 months for patients who are in the “active” group of the BABY HUG Follow-up Study.
*****For Patients who consented to having their blood stored.**

4.2 LABELS

The BABY HUG Follow-up Study Data Coordinating Center (DCC) will provide each Clinical Center with pre-printed labels for all specimens: blood, urine and images. The BABY HUG Follow-up Study labels are yellow with randomized 5-digit numbers to ensure the Core Laboratories remain "blind" to patient identification.

The Clinical Center staff will receive sets of label sheets grouped by Patient ID Number. When a child enrolls in the BABY HUG Follow-up Study, he/she maintains the Patient ID Number that was assigned to him/her in the BABY HUG Treatment Study. The set of label sheets with that Patient ID Number shall be used exclusively for that child for all of his/her specimens throughout the entire study. These child-specific label sheets enable the DCC to link a particular specimen to the child when the label number is entered in the database. A single label *number* is to be used per specimen.

Two sizes of labels (small and large) are provided. The small labels are to be used for tubes and vials. The labels in the first column have the Patient ID Number (e.g., 9998) and a label sequence number that is for DCC use. These labels will not be used. Each row on these label sheets consists of six duplicate labels with the same label number and label code. In general, a duplicate label (with the same label number) should be affixed to the specimen, the study form which requested the specimen, and the transmittal form for shipping the specimen. Cross off all unused labels in a row.

The large labels are to be used for all films (liver/spleen scans and abdominal sonograms). These label sheets have two unique label numbers, with 14 matching labels for each of the label numbers. The Patient ID Number and label sequence number are printed on the label in the first row of the label numbers and will not be used. In general, a matching label (with the same label number) should be affixed to all film sheets (e.g., if a child's liver/spleen scan results in 5 sheets of film, a label must be affixed to each of the five film sheets), the study

form which requested the image, and the transmittal form for shipping the films. Cross off all unused labels for a particular label number.

4.3 SHIPPING TRANSMITTAL FORMS

Study forms, transmittal forms and data files are used to track processing, shipment and receipt of biological specimens used in the follow-up study from Clinical Centers to Core Laboratories and the Central Repository. All blood specimens collected and shipped must be handled according to universal precautions.

All shipments to Core Laboratories must be accompanied by a transmittal form. Each Core Laboratory has a specific transmittal form (e.g., Form 100 is for all specimens sent to the Georgia Health Sciences University, Form 102 is for UTSW). Transmittal forms are accessed via the Forms Selection Process on the BABY HUG Follow-up StudyCTMS. (Please see Chapter 7.) Upon selection of the Core Laboratory, the appropriate transmittal form appears on the screen for data entry. Transmittal forms must be entered by 10:00 a.m. (Eastern Time) the day following specimen collection by the Coordinator.

Limited information is recorded on the transmittal forms. At a minimum, the Clinical Center number, the specimen label number (see Section 4.2) and the dates of collection and shipment are recorded. No patient identifiers are recorded. Single or multiple specimens from one patient are allowed on a single transmittal form. **Do not put multiple patients on a transmittal form.**

When printing the transmittal form, two copies are automatically printed; one copy should be kept in the patient's file and the other sent with the specimen(s). If a copy cannot be entered and/or printed in time for the specimen to be shipped, then a copy of a handwritten form must be sent with the specimen. The shipping information is listed on the form. All transmittal forms must be faxed to the Core Laboratory with the Federal Express tracking number before the shipment is sent.

4.4 HEMATOLOGY, BIOCHEMISTRY AND URINE SPECIMENS

4.4.1 Specimen Collection

All specimens are to be collected using **Standard Precautions**. The Core Laboratory can analyze specimens received up to 48 hours after collection. After this time, the specimens must be discarded. Clinical Centers will need to send specimens in a timely manner.

4.4.1.1 HbF

HbF is to be collected for patients in the active group only at 24 months.

4.4.1.2 HPLC Creatinine

HPLC Creatinine isto be collected for all patients at exit or 48 months (whichever comes first), and additionally for the active patients at 24 months.

4.4.1.3 Stored Blood Sample

For those who have consented, stored blood specimens will be collected at entry and at exit or 48 months, whichever comes first.

4.4.1.4 Urine for Microalbumin: Creatinine Ratio

Urine specimens are to be collected at entry and at exit or 48 months, whichever occurs first, for the urine Microalbumin: Creatinine ratio. Urine is to be transported in a cryovial and shipped to the GHSU Core Laboratory with the blood specimens. Please label the vial appropriately with a label provided by the DCC.

4.4.1.5. BUN

BUN results will be provided via Excel spreadsheet by the Clinical Center Coordinator, as abstracted from the participants' medical record.

4.4.2 Shipping Procedure

1. Gel packs must be frozen prior to shipping specimens to the GHSU Core Laboratory.
2. Place one frozen gel pack in the bottom of the styrofoam-lined shipping box.

3. Put the tubes (stored blood, creatinine HPLC, HbF and/or urine) in the foam insert located in the white plastic container, seal the plastic bag and tighten the orange lid.
4. Place the container inside the styrofoam-lined shipping box on top of the frozen gel pack.
5. Place another frozen gel pack on top of the plastic container.
6. Fill the void inside the shipping box with crumpled or shredded paper.
7. Cover the Styrofoam-lined box with the Styrofoam lid.
8. Fill out Transmittal Form 100. Include the FedEx Tracking Number on the transmittal form(s). All specimens can be shipped together in the same box.
9. FAX the transmittal form(s) to Niren Patel (706) 721-9637.
10. Insert the transmittal form(s) in the shipping box between the Styrofoam and the outer corrugated box.
11. Close the outer box and tape shut with appropriate shipping tape.
12. Attach a FedEx Airbill with the following address:

    Niren Patel (706) 721-9640
    Georgia Health Sciences University
    Hemoglobin Laboratory AC-1004
    1120 15th Street
    Augusta, GA 30912

13. If the shipment is not received in the GHSU Core Laboratory at the expected time, the Core Laboratory Coordinator or a designee will pursue tracking the shipment and notify the Clinical Center and the DCC.
14. Blood specimens not received within 48 hours of collection will not be processed and must be redrawn.

4.4.3 Stored Blood Aliquot Procedures

Stored blood specimens will require 5 mL collected in an EDTA lavender-top tube. Tube(s) must be labeled with the same 5-digit number using the labels provided by the DCC. The specimens will be divided into plasma and cell pellet aliquots and stored frozen -70° F at the Hematology Core Laboratory until shipped to the NHLBI Specimen Repository (BioLINCC). Additionally, this laboratory will conserve residual plasma and cell pellets, which will also be shipped to the NHLBI Specimen Repository (BioLINCC).

4.5 PIT COUNT

4.5.1 Preparation of Whole Blood Sample for Pitted Red Blood Cell Count

IMPORTANT: The pitted cell count sample should be prepared within one hour of collection of the blood sample into the EDTA lavender-top tube.

1. After the patient's whole blood sample is drawn and placed in an EDTA lavender-top tube, the sample is <u>immediately</u> used for preparation of the sample for the pitted cell count.
2. Put on gloves.
3. **Gently invert the lavender-top tube of patient blood 10 times to mix the sample.**
4. Remove stopper from the tube of blood.
5. Hold the provided plastic pipette vertically, squeeze the bulb and insert into the specimen. Carefully remove a small amount of the patient sample. Use a clean pipette for each patient sample. Wipe excess blood off of the outside of the pipette.
6. Place TWO <u>SMALL</u> DROPS (approximately 50 microliters) of the EDTA lavender-top tube blood into the plastic tube provided containing gluteraldehyde.
7. Recap the plastic glutaraldehyde tube firmly.
8. Gently invert the tube of blood/gluteraldehyde mixture ten times to ensure mixing

of specimen. Place into specimen bag.

9. Recap the EDTA lavender-top tube. Discard the pipette into a biohazard container.

10. Label the glutaraldehyde tube and bag with one of the child's five-digit label numbers. On a blank label provided by the DCC, write the date and time of preparation, and the initials of the person who prepared the sample. Record the same information on Form 102 (UTSW Transmittal Form).

11. Place the prepared sample in a refrigerator at 2^{o} - 8^{o} centigrade for storage until shipping, which must be accomplished within two weeks of collection.

4.5.2 Shipping Procedure

*** Please ship specimens on Monday through Thursday ONLY ***

1. Please contact John Burns to notify him of your intent to ship the (batched) specimen(s).
   a. Email contact john.burns@childrens.com preferred.
   b. Backup telephone number 214-456-6779 or if no answer 214-456-6065.
2. Use frozen gel packs for shipping the specimen.
3. Await telephone or email response (will occur within 1 working day) before shipping specimens.
4. If you do not receive a response to 2 separate messages please contact Leah Adix (BABY HUG Follow-up Study Data Manager) at 214-456-2888 or if unable to reach her, Zora R. Rogers, M.D. (Pitted Cell Count Core Laboratory PI) via 214-456-6102 to schedule the shipping.
5. Ship using the IATA-provided cold pack container with frozen gel packs to arrive the next morning (Tuesday - Friday only) to:

John Burns
Special Testing Laboratory
Children's Medical Center of Dallas
1935 Medical District Drive, D200
Dallas, Texas 75235

6. Enclose one copy of transmittal Form 102 with sample(s).
7. FAX a copy of the transmittal form to Leah Adix (BABY HUG Follow-up Study Data Manager) at 214-456-8469.
8. The Pitted Cell Core Laboratory will notify the Clinical Center upon receipt if specimens are not acceptable and need to be recollected at the next contact with the patient.

4.6 VDJ

Follow the procedure below for specimen preparation for VDJ:

1. Collect 3 mL of peripheral blood in an EDTA lavender-top vacutainer. This specimen can only be collected Monday - Thursday.
2. Affix one of the child's designated BABY HUG Follow-up Study labels to the tube.
3. Fill out Form 101 (St. Jude Transmittal Form), including the FedEx tracking number.
4. Fax the transmittal form to Thad Howard at (901) 595-4723.
5. Place a COLD (**not frozen**) gel pack above and below the container in the styrofoam package.
6. Place the transmittal form in the shipping box between the styrofoam and the outer corrugated box.
7. Ship at room temperature the day of collection using overnight delivery to:

Thad Howard
Room D2057, Danny Thomas Research Center
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 355
Memphis, TN 38105

4.7 HOWELL-JOLLY BODIES

Follow the procedure below for specimen preparation for HJB (same process as VDJ, different amount):

1. Collect 0.1 mL of peripheral blood in an EDTA lavender-top vacutainer. This specimen can only be collected Monday - Thursday.
2. Affix one of the child's designated BABY HUG Follow-up Study labels to the tube.
3. Fill out Form 101 (St. Jude Transmittal Form), including the FedEx tracking number.
4. Fax the transmittal form to Thad Howard at (901) 495-4723.
5. Place a cold (not frozen) gel pack above and below the container in the styrofoam package.
6. Place the transmittal form in the shipping box between the styrofoam and the outer corrugated box.
7. Ship at room temperature the day of collection using overnight delivery to:

Thad Howard
Room D2057, Danny Thomas Research Center
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 355
Memphis, TN 38105

4.8 CYSTATIN-C

Follow the procedure below for sample preparation for Cystatin-C:

1. Draw 0.5mL of blood into a small red-top (no anticoagulant) tube.
2. Hold the red-top tube at room temperature for 15-30 min (but not longer).
3. Centrifuge at 4^{o} C for 10 min in a refrigerated centrifuge at 800xG (approximately 3,000 RPM in most table top centrifuges) to separate the serum. If serum separation and recovery is not complete (less than 50% of initial volume), the sample can be re-spun, using the same conditions to recover more serum.

Centrifuge speeds are approximate, and can also be varied with the first or second spins to improve recovery, to optimize for the equipment being used.

4. Remove the serum without disturbing the cell contents (below) using a pipette, and transfer a 0.5 mL aliquot to a freezer vial (NUNC CryoTube polypropylene vials, Ext, starfoot, round 1.0 mL size, Cat # 375353)
5. Label the tube using a freezer-safe label provided by the DCC.
6. Freeze the specimen in a freezing vial and store at -70^{o} C.
7. Batch the specimen and ship to the laboratory on dry ice pellets by overnight carrier in the styrofoam container supplied. Include a completed transmittal Form 101.
8. The Core Laboratory should be notified by e-mail the night of shipment. The e-mail address is: thad.howard@stjude.org. Shipment should be made only Monday through Thursday.

The shipping address for Cystatin-C is:

Thad Howard
Room D2057, Danny Thomas Research Center
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 355
Memphis, TN 38105

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
BABY HUG FOLLOW-UP STUDY
MANUAL OF OPERATIONS

CHAPTER 5

PROCEDURES FOR SPECIAL STUDIES IN THE ACTIVE GROUP

5.1 INTRODUCTION

In addition to the collections specified in the BABY HUG Follow-up Study Protocol Section 9.2.1 for the passive group, active patients will also have the collection of many of the same primary and secondary endpoint measurements as in the BABY HUG Treatment Study. These will include: Hgb F, pit counts, HJB, liver-spleen scan information (quantitative and qualitative), abdominal sonogram, multi-digit serum creatinine (for the calculation of the Schwartz estimate of GFR), Cystatin C, and neuropsychological testing. Note that the tests and procedures described in this chapter apply only to the active group of patients in the follow-up study.

The schedule of child visits during which specimens will be collected for laboratory testing is shown in Appendix A of the Protocol (Exhibit 1-1). As permitted by the family, primary and secondary endpoints will be measured four years after the child's randomization (two years after exit) in the BABY HUG Treatment Study as well as one behavioral test measurement (Vineland) four years after exit from the BABY HUG Treatment Study. This schedule is designed to measure all endpoints along the combined continuum of treatment and visits at follow-up study start and at two and four years later.

5.2 LIVER-SPLEEN SCAN

5.2.1 Procedure

Radiopharmaceutical:	99m Tc Sulfur Colloid.
Dose:	0.05 mCi/kg (preferred minimum dose 0.5 mCi; a dose of 1.0 mCi or more acceptable if that is the local practice).

Injection Site:		Direct venous administration. Scan should begin within 15 minutes of injection.
Equipment:		Large field of view camera.
Collimator:		Dual Detector (have consistent use of collimator type for a patient).
Computer Set up:		**400K Image:** Static 400 K counts, 256 X 256 byte mode. **Timed Image:** Static fixed time views for the same amount of time as the static 400K counts true posterior image.
Scanning Technique:	1.	Patient in supine position on table. Collimator should be in contact with patient (anterior head touching or as close as possible).
	2.	400K Image: **true anterior/posterior** views. Timed Image: **left anterior oblique/right posterior oblique** views (obliquity should create maximum separation of liver and spleen with minimal to no overlap of organs; record camera angle).
Quantitative Analysis:	1.	400K Image: Draw region of interest around spleen, then liver on the **anterior** view. Record counts, number of pixels in ROI, and counts/pixel for each organ. Take a picture.
	2.	400K Image: Repeat the same for the **posterior** view. Take a picture.
	3.	400K Image: Calculate the geometric mean counts of spleen and liver from both views. (See Section 5.2.2.) Do the same for counts/pixel. Take a picture or record on film.
	4.	400K Image: Generate the total spleen to liver ratio (See Section 5.2.2.) and the counts/pixel spleen to liver ratio. Take a picture(s) or record on film.
	5.	Timed Image: Repeat step 1 using **left anterior oblique** view.
	6.	Timed Image: Repeat step 1 using **right posterior oblique** view.
	7.	Timed Image: Calculate the geometric mean counts of spleen and liver from both views. Do the same for counts/pixel. Take a picture or record on film.
	8.	Timed Image: Generate the total spleen to liver ratio and the counts/pixel spleen to liver ratio. Take a picture(s) or record on film.
Processing Scans:	1.	400K Image:

- Include proper identification
- Label the anterior view #1.
- Label the posterior view #2.
- Label the anterior view with region of interest around spleen and liver with counts and counts/pixel recorded on the film as #3.
- Label the posterior view with region of interest around spleen and liver with counts and counts/pixel recorded on the film as #4.
- Label as #5 the geometric mean counts and the geometric mean counts/pixel of spleen and liver from both views.
- Label as #6 the total counts and counts/pixel spleen to liver ratios.

2. Timed Image:

- Include proper identification.
- Label the left anterior oblique (LAO) view #7.
- Label the right posterior oblique (RPO) view #8.
- Label the LAO view with region of interest around spleen and liver with counts and counts/pixel recorded on the film as #9.
- Label the RPO view with region of interest around spleen and liver with counts and counts/pixel recorded on the film as #10.
- Label as #11 the geometric mean counts and geometric mean counts/pixel of spleen and liver from both views.
- Label as #12 the total counts and counts/pixel spleen to liver ratios.

5.2.2 Calculations for Quantitative Assessment

The geometric mean counts of the spleen and the liver, and the spleen-liver ratio, will be recorded on the films and calculated according to the following formula:

Spleen geometric mean = $\sqrt{AxC}$

Liver geometric mean = $\sqrt{BxD}$

Spleen-liver ratio = $\frac{\sqrt{AxC}}{\sqrt{BxD}}$

For the total counts of spleen-liver ratios (400K and Timed Images), the following applies:

A = anterior (400K Image) or LAO (Timed Image) spleen count

B = anterior (400K Image) or LAO (Timed Image) liver count

C = posterior (400K Image) or RPO (Timed Image) spleen count

D = posterior (400K Image) or RPO (Timed Image) liver count

The counts/pixel geometric means and the spleen-liver ratios (400K Image and Timed Image) will also be calculated according to the above formula.

5.2.3 Labeling and Shipping of Film Sheets

A hard copy of the liver/spleen scan film sheets must be sent to the Data Coordinating Center (DCC). The DCC will forward all film sheets to two central reviewers to assess splenic uptake. Use the following procedure to label and ship all the film sheets:

1. Obscure all patient identifying information on all film sheets.

2. Affix to each film sheet a duplicate label with the same 5-digit number as affixed to the BABY HUG Follow-up Study form requesting the scan (Form 21). All film sheets must have the same label number.

3. Complete Transmittal Form 103 (DCC Transmittal Form). Affix to it a duplicate label with the same 5-digit number as already affixed to the BABY HUG Follow-up Study Form 21 and the film sheets.

4. Send all film sheets and Transmittal Form 103 within 5 days of the film date via FedEx to the Data Coordinating Center:

BABY HUG Follow-up Coordinator
Clinical Trials & Surveys Corp.
10065 Red Run Blvd., Suite 250
Owings Mills, MD 21117-4848

5.3 ABDOMINAL SONOGRAM

5.3.1 Procedure

<u>Scheduling and NPO Guidelines</u>

Because it is preferable that patients be NPO (except for clear liquids) for six hours before the sonogram, schedule them as the first exam of the day. It is acceptable to give them clear

liquids (Pedialyte, water, clear juices) as needed, no milk, prior to the sonogram, as indicated by each Clinical Center's standard of care.

Probe Selection

Use the highest frequency, non-linear probe that is available and that gives the best image quality.

Image Annotation

When the patient is not supine, note on the image the position that the patient is in (i.e. left decubitus, right decubitis, prone or upright).

Scanning Protocol

A. Gall Bladder

i. With the patient in the supine position, take multiple longitudinal and transverse images representative of the entire gallbladder.

ii. With the patient in either the left or right lateral decubitus position, take multiple transverse and longitudinal images representative of the entire gallbladder.

iii. If there appears to be gallbladder wall thickening (above 3mm) measure the gallbladder wall on a transverse image and obtain a color Doppler image of the gallbladder wall.

iv. Measure the diameter of the common bile duct (CBD) in the region of the porta hepatitis. Confirm that you are measuring the CBD with color Doppler.

B. Liver

i. Include one longitudinal image of the liver obtained with the right kidney in the field of view. The image should be obtained through the middle portion of the kidney and/or where the greatest kidney length can be

obtained. Please include a longitudinal measurement of the liver at this location.

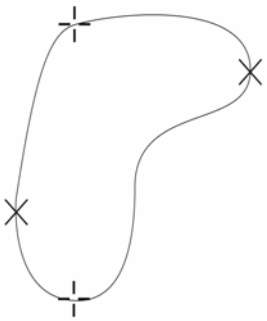
C. Spleen (See Exhibit 5-1 for the complete checklist.)

i. Obtain measurements during relaxed respiration.

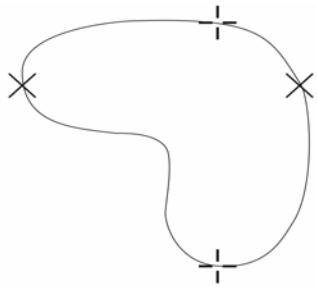
ii. In the coronal plane, measure the greatest length and AP diameter at the hilum of the spleen.

iii. In the transverse plane, measure the greatest transverse diameter of the spleen at the level of the hilum.

iv. Multiply the above three measurements together then multiply the result by a factor of 0.53 to obtain an estimate of spleen volume.



Example of a longitudinal spleen image: Note the correct cursor placement for anterior-posterior measurement (+) and longitudinal measurement (x).



Example of a transverse image of the spleen: Note the correct cursor placement for anterior-posterior measurement (+) and transverse measurement (x).

D. Kidneys

i. In the supine position, obtain a longitudinal image of each kidney with the liver and spleen in the field of view in order to compare renal echogenicity to liver/spleen echogenicity.

ii. For the remainder of renal scanning, place the patient prone whenever possible. Alternatively, if necessary, scan in the upright position, with the probe on the patient's back. If unable to scan with a posterior approach, scan the kidneys in the supine position. Obtain the following:

1. Longitudinal images representative of the entire kidney
2. Transverse images representative of the entire kidney
3. Maximum renal length measurements

iii. Maximum transverse measurement at the level of the renal hilum

iv. Maximum anterior-posterior measurement in BOTH the longitudinal and transverse planes

5.3.2 Labeling and Shipping of Film Sheets

A hard copy of the abdominal sonogram film sheets or a CD (no more than 12 images per sheet) must be sent to the DCC. The DCC will forward all film sheets or CD to a central reviewer. Use the following procedure to label and ship all the film sheets:

1. Obscure all patient identifying information on all film sheets or CDs.
2. Affix to each film sheet or CD a duplicate label with the same 5-digit number as affixed to the BABY HUG Follow-up Study form requesting the sonogram. All film sheets must have the same label number.

3. Complete Transmittal Form 103 (DCC Transmittal List). Affix to it a duplicate label with the same 5-digit number already affixed to the BABY HUG Follow-up Study Form 23 and the film sheets.
4. Send all film sheets or CDs and Transmittal Form 103 within 5 days of the film date via FedEx to the Data Coordinating Center:

   BABY HUG Follow-up Coordinator
   BABY HUG Data Coordinating Center
   Clinical Trials & Surveys Corp. (C-TASC)
   10065 Red Run Blvd., Suite 250
   Owings Mills, MD 21117-4848

5.4 WECHSLER PRESCHOOL AND PRIMARY SCALE OF INTELLIGENCE (WPPSI)

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) is an intelligence test designed for children ages 2 years 6 months to 7 years 3 months.

The current revision from 2002, WPPSI–III, is published by Harcourt Assessment. It provides subtest and composite scores that represent intellectual functioning in verbal and performance cognitive domains, as well as providing a composite score that represents a child's general intellectual ability (i.e., Full Scale IQ).

5.4.1 Subtests

The WPPSI–III is composed of 14 subtests.

- Block Design - While viewing a constructed model or a picture in a Stimulus Book, the child uses one- or two-color blocks to re-create the design within a specified time limit. Information - For Picture Items, the child responds to a question by choosing a picture from four response options. For Verbal Items, the child answers questions that address a broad range of general knowledge topics.
- Matrix Reasoning - The child looks at an incomplete matrix and selects the missing portion from 4 or 5 response options.

- Vocabulary - For Picture Items, the child names pictures that are displayed in a Stimulus Book. For Verbal Items, the child gives definitions for words that the examiner reads aloud.
- Picture Concepts - The child is presented with two or three rows of pictures and chooses one picture from each row to form a group with a common characteristic.
- Symbol Search - The child scans a search group and indicates whether a target symbol matches any of the symbols in the search group.
- Word Reasoning - The child is asked to identify the common concept being described in a series of increasingly specific clues.
- Coding - The child copies symbols that are paired with simple geometric shapes. Using a key, the child draws each symbol in its corresponding shape.
- Comprehension - The child answers questions based on his or her understanding of general principles and social situations.
- Picture Completion - The child views a picture and then points to or names the important missing part.
- Similarities - The child is read an incomplete sentence containing two concepts that share a common characteristic. The child is asked to complete the sentence by providing a response that reflects the shared characteristic.
- Receptive Vocabulary - The child looks at a group of four pictures and points to the one the examiner names aloud.
- Object Assembly - The child is presented with the pieces of a puzzle in a standard arrangement and fits the pieces together to form a meaningful whole within 90 seconds.
- Picture Naming - The child names pictures that are displayed in a Stimulus Book.

5.4.2 Administration

Administered according to procedures in the WPPSI-III manual, children in the 2:6-3:11 age band are administered only five of the subtests: Receptive Vocabulary, Block Design, Information, Object Assembly, and Picture Naming.

5.4.3 Scoring

The WPPSI–III provides Verbal and Performance IQ scores as well as the Full Scale IQ. The Processing Speed Quotient will be derived for children aged 4:0 – 7:3.

A General Language Composite can be determined for children in both age bands (2:6–3:11 & 4:0–7:3). The children in the 4:0–7:3 age band are to be administered the following subtests: Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts and Coding. These subtests are optional: Receptive Vocabulary, Picture Naming and the supplemental test Object Assembly.

5.5 Vineland Adaptive Behavior Scales

A BABY HUG Follow-up staff member at each Clinical Center will administer the *Vineland Adaptive Behavior Scales: Interview Edition* to the child's parent or guardian at the 48 Month visit for Active patients only.

The Data Coordinating Center (DCC) will purchase sufficient Record Booklets for each Clinical Center.

The BABY HUG Follow-up staff member will administer the Communications Daily Living Skills, Socialization and Motor Skills Domains to the child's parent or guardian. The BABY HUG Follow-up staff member should strictly adhere to the standardized directions given in the Survey Form Manual for administration of the questionnaire. The responses are to be recorded and scored on the Record Booklet by the staff member administering the test, and then transferred to BABY HUG Follow-up form 27 (Vineland) by the staff member. The Standard Score, the 95% Band of Error and the National Percentile Rank must also be recorded on the booklet and the BABY HUG Follow-up form. If the child is older than 5 years old, then

the Motor Skills section of the examination should be skipped and documented as “Not Done” on the Form 27.

Within 24 hours of completion of the Vineland test, the completed BABY HUG Follow-up Form 27 is to be data entered in StudyCTMS. All original examination forms should be kept in the research files of the study following institutional IRB and HIPPA policies related to the storage and maintenance of psychological testing raw data.

If a child’s parent/guardian would like the results of the examination, they can request it.

5.6 MRI, MRA, CT, TCD and Neuropsychological Tests

If a patient has any MRI, MRA, CT, TCD or Neuropsychological tests (other than the WPPSI at 24 months and the Vineland at 48 months for active patients) performed during the course of the BABY HUG Follow-up Study, include a copy of the accompanying reports in the data abstractions done every 6 months.

5.7 Sending Imaging and Neuropsychological Reports

Use Transmittal Form 105 (see exhibit 7-1) in order to fax hard copy MRI, MRA, CT, TCD and Neuropsychological Reports. Up to four reports for one patient can be faxed on each transmittal form.

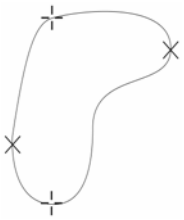
EXHIBIT 5-1
CHECKLIST FOR BABY HUG FOLLOW-UP ABDOMINAL SONOGRAPHY

Spleen (see diagrams below)

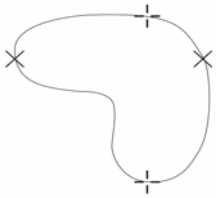
- ☐ In the coronal plane, measure at the level of the hilum:
  - ☐ Length
  - ☐ AP diameter
- ☐ In the transverse plane, measure at the level of the hilum:
  - ☐ Transverse

Proper placement of cursors for spleen measurements

.



LONGITUDINAL



TRANSVERSE

Kidneys

- ☐ In the supine position obtain a longitudinal image of each kidney with liver/spleen in field of view for comparison of echogenicity..
- ☐ In the prone position obtain:
  - ☐ Longitudinal images of the entire kidney
  - ☐ Transverse images of the entire kidney
  - ☐ Maximum renal length measurement
  - ☐ AP measurement in BOTH longitudinal and transverse planes.
- ☐ At level of renal hilum:
  - ☐ Transverse measurement

Gall bladder

- ☐ Obtain longitudinal and transverse images of entire GB in supine position.
- ☐ Obtain longitudinal and transverse images of entire GB in decub position.
- ☐ If GB wall thickening >3 mm:
  - ☐ Measure GB wall on transverse image
  - ☐ Obtain color Doppler image of GB wall
- ☐ Measure common bile duct in region of the porta hepatis.
  - ☐ Confirm measurement with color Doppler.

Liver

- ☐ With right kidney in field of view, measure the liver length where the greatest length can be obtained.

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CHAPTER 6

CENTRAL READING GROUPS

6.1 INTRODUCTION

Liver-spleen scans and abdominal ultrasounds will be centrally evaluated by individuals independent of the BABY HUG Clinical Centers for future review. The procedures for central review are described in this chapter.

6.2 LIVER-SPLEEN SCAN

6.2.1 Overview

The liver spleen scans will be read by two nuclear medicine specialists who will independently assess each liver/spleen scan that is performed at 24 months after exit from the BABY HUG Treatment Study as having normal, decreased or absent spleen function. In case of disagreement, a scan will be sent to a third reviewer. The two readings out of the three that are in agreement will be the single final reading. This qualitative assessment of spleen function will be used for determining the primary endpoint outcome: worsened or not worsened (includes improved) spleen.

If a patient has had a splenectomy, the liver-spleen scan is not required.

6.2.2 Scans Required for Central Reading

Scans will meet the following specifications.

<u>400K Image</u>

- Proper identification (Patient 5-digit label number and date)
- An anterior view labeled #1
- A posterior view labeled #2
- An anterior view with region of interest around spleen and liver with counts and counts/pixel recorded on film labeled #3

- A posterior view with region of interest around spleen and liver with counts and counts/pixel recorded on film labeled #4
- The geometric mean counts and the geometric mean counts/pixel of spleen and liver from both views calculated and recorded on film labeled #5
- The total and counts/pixel spleen to liver ratios recorded on film labeled #6

Timed Image

- Proper identification (Patient 5-digit label number and date)
- A left anterior oblique (LAO) view labeled #7
- A right posterior oblique (RPO) view labeled #8
- A LAO view with region of interest around spleen and liver with counts and counts/pixel recorded on film labeled #9
- A RPO view with region of interest around spleen and liver with counts and counts/pixel recorded on film labeled #10
- The geometric mean counts and geometric mean counts/pixel of spleen and liver from both views calculated and recorded on film labeled #11
- The total and counts/pixel spleen to liver ratios recorded on film labeled #12

6.2.3 DCC Scan Processing Procedure

Clinical Center staff will forward one copy of each film to the Data Coordinating Center (DCC) with a transmittal form (BABY HUG Follow-up Form 103). The DCC will log receipt of the films, and forward them to one of the reviewers with a blank Liver-Spleen Scan Central Reading Form (Form 31). The grader will complete the Form 31 and return the films and the form to the DCC. The DCC will then forward the films to the other reviewer with a blank Form 31; the second grader will complete the Form 31 and return the films and the form to the DCC. DCC coordination staff will data enter the forms. DCC computing staff will compare the two gradings. If they agree, the spleen reading is final. If they disagree, the scan will be sent to a third

reviewer. On receipt of the third reading, a single final reading will be the two readings that agree. At the end of the study, the spleen primary outcome (improved, not worse or worse) will be computed by DCC statistical staff at the time of interim and the final data analysis.

If a reader determines that the scans are not of sufficient quality to be evaluated (Form 31, Part II, Item 3: Current status of this reading), the scans are returned to the DCC with an explanation and a recommendation for the Clinical Center. If a liver-spleen scan as submitted is judged to be inadequate for reading, it will be returned to the Clinical Center for reprocessing if possible. If reprocessing is not possible, a repeat scan will not be performed (unless IRB approval is obtained) and no final grading will be available.

6.2.4. Guidelines for Qualitative Grading of Liver-Spleen Scans

The central readings will be based on qualitative, visual assessments comparing uptake in the spleen to that in the liver. The reader will rate the spleen uptake on the posterior and LAO views, as compared to uptake in the left lobe of the liver and provide a qualitative assessment of spleen function. The measurement will be recorded on Form 31 (Liver-Spleen Scan Central Reading) as follows:

- *Normal*: normal spleen function (uptake proportionate to liver);
- *Decreased:* spleen function but decreased (uptake disproportionately lower than liver);
- *Absent:* spleen function absent (no appreciable uptake above background level.

6.2.5 Liver-Spleen Primary Outcome

The readings as applied in Table 6-1 determine for each child whether spleen function has improved, worsened or not worsened after exit from the BABY HUG Treatment study. These three categories (Improved, Not Worse, and Worse) contribute to the possible responses for the spleen primary outcome.

TABLE 6-1
Liver-Spleen Primary Outcome Determination

Spleen Function at Baseline	Spleen Function After Exit from the treatment study		
	Normal	*Decreased*	*Absent*
Normal	**Not worse**	**Worse**	**Worse**
Decreased	**Improved**	**Not Worse**	**Worse**
Absent	**Improved**	**Improved**	**Not Worse**

6.2.6 Guidelines for Quantitative Grading of Liver-Spleen Scans

A quantitative assessment of liver-spleen uptake will provide additional information about spleen function that may be used as a secondary endpoint in the data analysis. The total count spleen-liver geometric means and ratio will be recorded on the films for both the 400 K Image and Timed Image. The counts/pixel spleen-liver geometric means and ratios (400K Image and Timed Image) will also be calculated. A spleen-liver ratio greater than 0.2 using total counts is often considered normal, while below 0.2 is often considered reduced splenic function. Using counts/pixel, a spleen-liver ratio in the 0.7-0.9 range is considered normal.

6.3 ABDOMINAL ULTRASOUND

6.3.1 Overview

Abdominal ultrasound imaging will be performed at 24 months after exit from the BABY HUG Treatment Study. The evaluation is tailored specifically to determine splenic volume and echogenicity, renal volumes and echogenicity and to assess the gallbladder and biliary system. The imaging will be centrally reviewed by one pediatric radiologist.

6.3.2 Assessment of the Spleen

6.3.2.1 Splenic Parenchyma

Representative images of the entire spleen will be obtained in the longitudinal and transverse planes and the parenchyma will be assessed for normal vs abnormal echogenicity.

6.3.2.2 Splenic Volume

Table 6-2 shows normal values to use to evaluate splenic volume [1].

TABLE 6-2
Splenic Volume

Body length	Splenic Volume Mean values	Standard deviation
56 - 70 cm	18.02 cc	7.54
71 - 85 cm	29.63 cc	14.48
86 -100 cm	32.53 cc	16.09
101-110 cm	30.29 cc	7.24
111-120 cm	50.27 cc	15.2
121-130 cm	43.52 cc	12.73
131-140 cm	60.07 cc	18.86
141-150 cm	56.74 cc	24.07
151-160 cm	75.85 cc	10.65
161-170 cm	74.80 cc	18.20

6.3.3 Assessment of the Kidneys

6.3.3.1 Renal Parenchyma

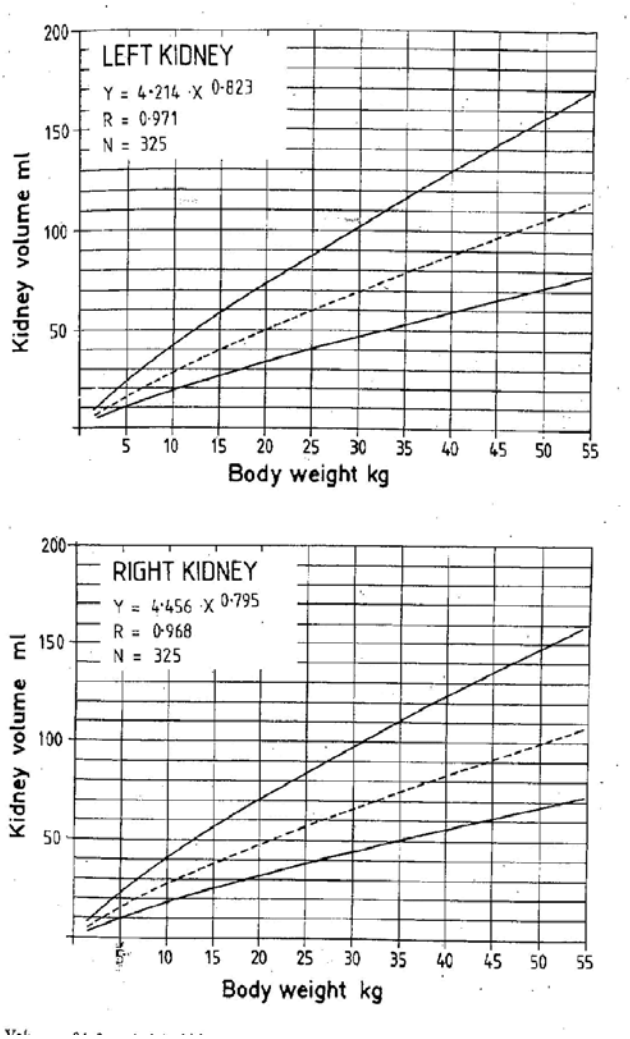
Representative images of both kidneys will be obtained in the longitudinal and transverse planes and the cortical echogenicity will be determined to be either normal or abnormal.

6.3.3.2 Renal Volume

Figure 6-3 will be used as standards to evaluate the renal volumes [2].

Figure 6-3

Kidney Volume



6.3.4 Gall Bladder and Biliary System

The gall bladder wall will be considered abnormally thickened when it measures > 3 mm. The common bile duct will be considered to be dilated when it measures > 4 mm.

6.3.5 Liver

There are no published normal liver lengths or volumes for children. For purposes of determining whether the liver is enlarged, a comparison of the liver length to the length of the right kidney will be used. If the inferior tip of the liver extends below the inferior tip of the right

kidney on a longitudinal image obtained in the region of the right kidney with the longest dimension, the patient will be considered to have hepatomegaly.

6.3.6 Processing Scans for Central Reading

The ultrasound images will contain the following information

- Proper identification (Patient 5-digit label number and date)
- The probe frequency
- Annotate the image with the position of the patient if other than supine/recumbent
- Annotate the image as transverse or longitudinal
- Measurements of the spleen in the transverse, anterior-posterior and longitudinal dimensions
- Measurements of the kidneys in the longitudinal, transverse and anterior-posterior dimensions
- Measurement of the gall bladder wall
- Measurement of the common bile duct in the region of the porta hepatis

6.3.7 Handling the Ultrasound Images

Clinical Center staff will forward original ultrasound images to the DCC with Form 103 (DCC Transmittal Form). Images will be provided on hard-copy film or CD with no more than 12 images per sheet (14" X 17") of film.

The ultrasound images will be accompanied by the following information:

- Proper Identification (Patient 5-digit label number and date)
- Patient's Age
- Patient's Body Length
- Patient's Body Weight
- NPO Status (how long they were held NPO)

The DCC will log receipt of the films, and forward them to the central reader with a blank Abdominal Sonogram Reading Form (Form 33). The reader will complete Form 33 and return the films/CD and form to the DCC. DCC coordination staff will data enter the form.

6.4 TRANSCRANIAL DOPPLER (TCD) EXAM

It is anticipated that most children will have at least one TCD study during the follow-up period. The TCD evaluations will be performed according to each Clinical Center's standard of care. The study performed as part of clinical care **closest to two years** from the date the patient completed the BABY HUG treatment study will be copied and sent for review and analysis by the TCD reading committee. The identification of this exam can be done during the data abstraction review.

6.4.1 TCD Exam Form

Once the appropriate TCD has been identified, BABY HUG Follow-up Form 13 (TCD Exam) will be completed by the coordinator. The coordinator will affix one of the patient's label numbers to the form. Form 13 will remain with the patient's binder at the BABY HUG Follow-up Clinical Center.

6.4.2 Processing the TCD Exam

Have the TCD examiner copy the TCD exam. A copy of the TCD diskette will be left at the BABY HUG Follow-up Clinical Center. The coordinator will affix a duplicate label (with the same label affixed to Form 13) to the TCD diskette.

6.4.3 Sending the TCD Exam

Each Clinical Center will be given FedEx billable stamps for sending the TCD diskette to the Medical University of South Carolina (MUSC). The coordinator will complete Form 104 (TCD Transmittal Form) found on the www.studyctms.com website for the BABY HUG Follow-up Study.

Fax the form, then copy it to send in the package with the TCD diskette to the MUSC.

6.4.4 TCD Reading and Archiving

The TCD exam will be read and interpreted using standardized procedures by the TCD Center at the MUSC.

After MCG staff interprets the exam, the results will be sent to the DCC for record retention and statistical analysis of the subject population for the BABY HUG Follow-up Study.

MUSC will retain the diskette for archiving with the BABY HUG Follow-up Study records.

6.5 REFERENCES

1. Dittrich M, Milde S, Dinkel E, Baumann W, Weitzel D. Sonography biometry of liver and spleen size in childhood. Pediatr Radiol (1983) 13:206-211.
2. Dinkel M, Ertel M, Dittrich M, Peters H, Berres M, Schulte-Wissermann H. Kidney size in childhood: Sonographical growth charts for kidney length and volume. Pediatr Radiol (1985) 15(1):38-43.

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CHAPTER 7

DATA COLLECTION, ENTRY, EDITING, STORAGE AND ARCHIVAL

7.1 CLINICAL CENTER DATA

7.1.1 Data Collection

The Data Coordinating Center (DCC) is the repository of all data. All BABY HUG Follow-up data collection forms and transmittal lists (for blood specimens and other materials [e.g., images] shipped in the course of BABY HUG Follow-up data collection) will be sent to the DCC via StudyCTMS.

Data collection at the Clinical Centers, and core laboratory and central reader results, will provide the data set to answer the study's primary objectives and key questions. It is imperative that all the data be captured and sent to the DCC on the expected dates. The expected dates for completed forms are as follows:

- One week for all forms (e.g. the study entry visit for Form 03, all imaging study transmittal forms)
    - Use Transmittal Form 105 for imaging reports such as MRI, MRA, TCD, CT and Neuropsychology Reports.
- Prior to shipment (day of collection or batched) for all specimen and special test transmittal forms (e.g. abdominal sonogram films)

Coordinators may want to keep a supply of blank study forms in a file drawer, in folders labeled with the form number. Paper copies of the forms can be printed off the BABY HUG Follow-up website by accessing Forms on the BABY HUG Follow-up home page (see Chapter 14). As information is gathered by medical record review, it can be recorded on the appropriate form. These can be considered working data collection forms, which will provide the information necessary for Internet data entry.

Each study form MUST have a source document. The source document may be electronic or hard copy. The source document must be one of the following:

- Data Abstraction Forms – Medical record
- Special Studies – (Liver/Spleen, abd sono), handwritten CRF
- Neuropsychology – WPPSI and Vineland test booklets
- Local Laboratory results – lab printout
- Clinically ordered studies (e.g., TCD) – printed report

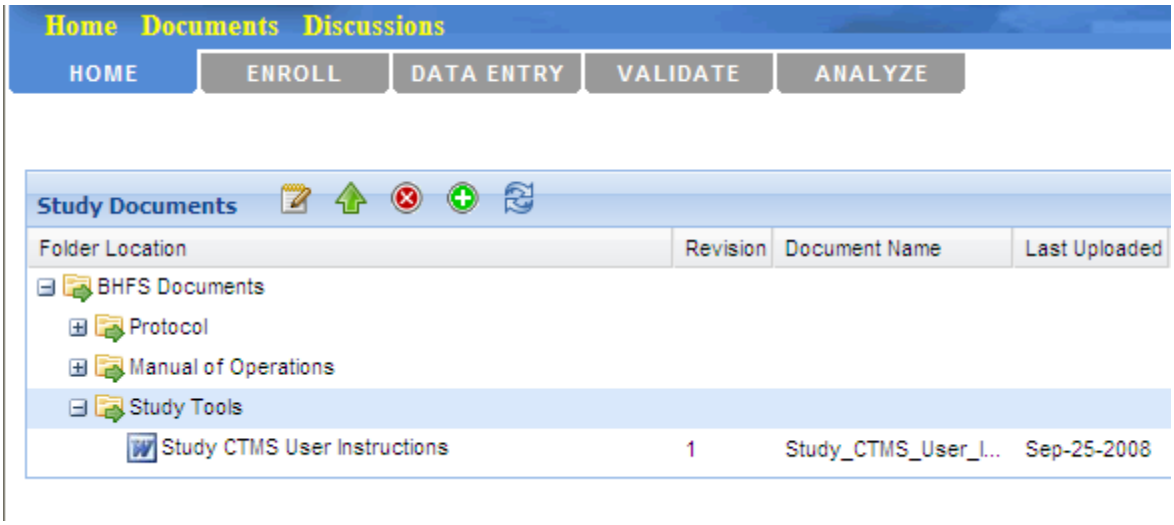
All source documents must be signed and dated. All modifications to the source document must be properly recorded (single-line strikeout so that the original text is still readable, initialed and dated, or similar process electronically, dependent upon your Center's electronic system formatting). The study source material must be kept in a manner acceptable for regulatory purposes.

Electronic source documents will be considered the same as paper source documents in accordance with each State's regulations.

7.1.2 Data Entry

Accurate data entry is crucial to the success of the study. All of the report forms for data entry are on the BABY HUG Follow-up website. QxQs for each of the forms are also on the website. StudyCTMS has been developed to allow entry of data as it becomes available and preliminary editing at the time of data entry. The data are registered in the central database immediately after saving the data.

To aid in learning about StudyCTMS, a training manual has been written for all Clinical Centers to reference entitled “User Instructions: StudyCTMS”. You can find it in the Documents page within StudyCTMS:



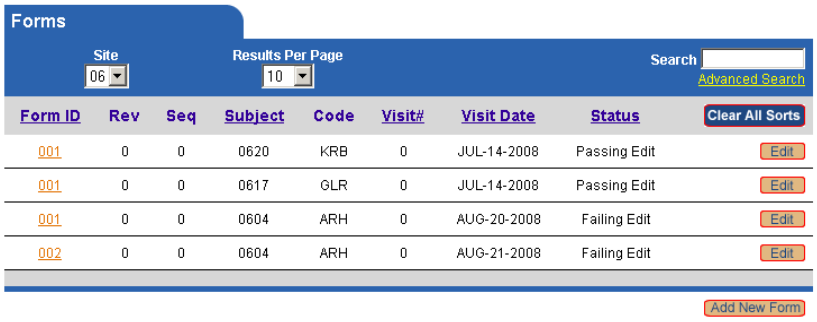
7.1.2.1 Internet Data Entry System User Access

Before you can enter data into StudyCTMS, you must be authorized to have Data Entry and Content use of the BABY HUG Follow-up system (see Chapter 14). The contents of the BABY HUG Follow-up website, including the computer system requirements to access the site, are described in Chapter 14. The DCC will send each certified user a permanent username and password, which will be required for data entry for those new to the BABY HUG Follow-up Study. Clinical Center staff continuing in the BABY HUG Follow-up Study from the BABY HUG Treatment Study will retain their current authorization for the BABY HUG Follow-up website and receive a new username and password for the follow-up study.

7.1.2.2 Form Selection

StudyCTMS has a complete Electronic Data Capture (EDC) system built in. From the Visit Forms area, users may view already-entered forms, edit forms (if they have rights), search for forms, or enter data into a new form.

When a user arrives at the Visit Forms page he/she will be provided a complete list of all forms that have previously been entered for their site.



Once you have identified an existing form you would like to view, simply click on the Form ID to the left of the form you want to view. This will launch the form in view-only mode. The form will be fully functional showing all form tabs, form QxQ's, field values, errors and error codes.

7.1.2.3 Entering Study Form Data

Identifying Information Fields. Identifying information includes:

- Site Number where the child was being followed when he/she exited the BABY HUG Treatment Study
- Patient Identification Number
- Patient Letter Code
- Visit
- Sequence Number (Enter 0 in this field. It is a standard field for StudyCTMS, but does not apply to the BABY HUG Follow-Up Study.)
- Date

After entering all the identifying information, press the <Enter> key or click on OK. The system then performs a check of the patient identifying data. A message box will pop up if there is an identifying information error. Select the OK button to clear the message box. Common identifying information errors are:

- The patient does not exist in the system

- The Letter Code is wrong
- Incorrect visit
- Date is greater than today
- Out of acceptable time window

Study Data Fields.

Bubbles: Click on the bubble to select an answer. To change an answer, click on another bubble. To remove a response, click on the 'clear' bubble.

Write-in items: If completely filled they will auto-skip to next item; if not completely filled in, press <enter>.

Check boxes: Click on boxes to toggle between on/off.

Signature Field. Do not try to key the signature. Click on the check box if the signature exists or leave the check box un-clicked if no signature exists. Ideally, two signatures will be obtained: one from the person responsible for entering the data on the form, and the other for the person who acquired the data.

Form Entry Tips.

- Use the Page Tabs (1, 2, 3, etc.) located on the top of the data entry screen.
- Use the Scroll Bar at the right side of the data entry screen to move down the page.
- Watch for informational and error messages as you tab through the form and upon clicking the "submit" button. An example of an error message is "Not a valid date format". This indicates that the format entered for the date is not correct. Dates should be entered in MON-DD-YYYY format, using the first three letters of the month.

7.1.2.4 Entering Transmittal Form Data

Once a transmittal form is selected, StudyCTMS will automatically populate the Core Laboratory name and the Clinical Center number data fields. The ship date will also be automatically populated with the current date; this date can be modified if the ship date is not the current date.

All the data fields are write-in items. If they are completely filled in, they will auto-skip to the next item; if not completely filled in, press <enter>. Type in the name and certification number of the Clinical Center staff member preparing the transmittal form. If the FedEx tracking number is known, enter it. Any comments about the specimens or the shipment may be entered in the comments field. The 5-digit label number can be either typed in or selected from the pop-up box. All transmittal forms require the specimen date, and some require additional information for processing.

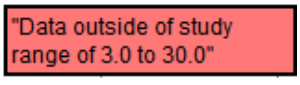
7.1.2.5 Save Your Work

If all the data are keyed, Click the "Submit" button at the bottom of the form. This will post your data to the form and save the data you keyed to the database.

7.1.2.6 Forms That Fail Edit

StudyCTMS edits forms through its "Validate Forms" feature. The validate forms feature provides a list of all forms with errors including a count of the error present. From the Validate Forms page users can sort, search and view forms in the exact same manner as described in the Form List section except that ALL results shown will only include forms that contain at least one non-validated error.

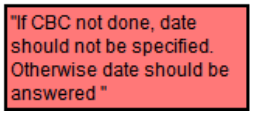
The Error column shows a count of all form errors that have NOT been validated or corrected to date. To enter a form to edit, the user clicks on the **Edit** button to the right of the form they desire to edit.

When the form appears, all errors will be shown with one of two icon types. All range errors (data entry, human and study) are shown using an exclamation point icon  . If the user hovers over this icon, they will be presented with a description of the range error including the valid range. 

All consistency errors appear as a colored square with a number. The number indicates the consistency error group and the color makes a visual connection between related fields with

errors. For example, a consistency check with  next to it indicates that this field and any other fields with that same icon present are part of a consistency error. Any one form may have any number of consistency errors impacting any number of fields. One field on any form can also be part of any number of consistency errors and may, therefore, have multiple square, numbered icons next to it.

Hovering over a consistency error will reveal a message box describing the error.



7.1.2.7 Internet Failure

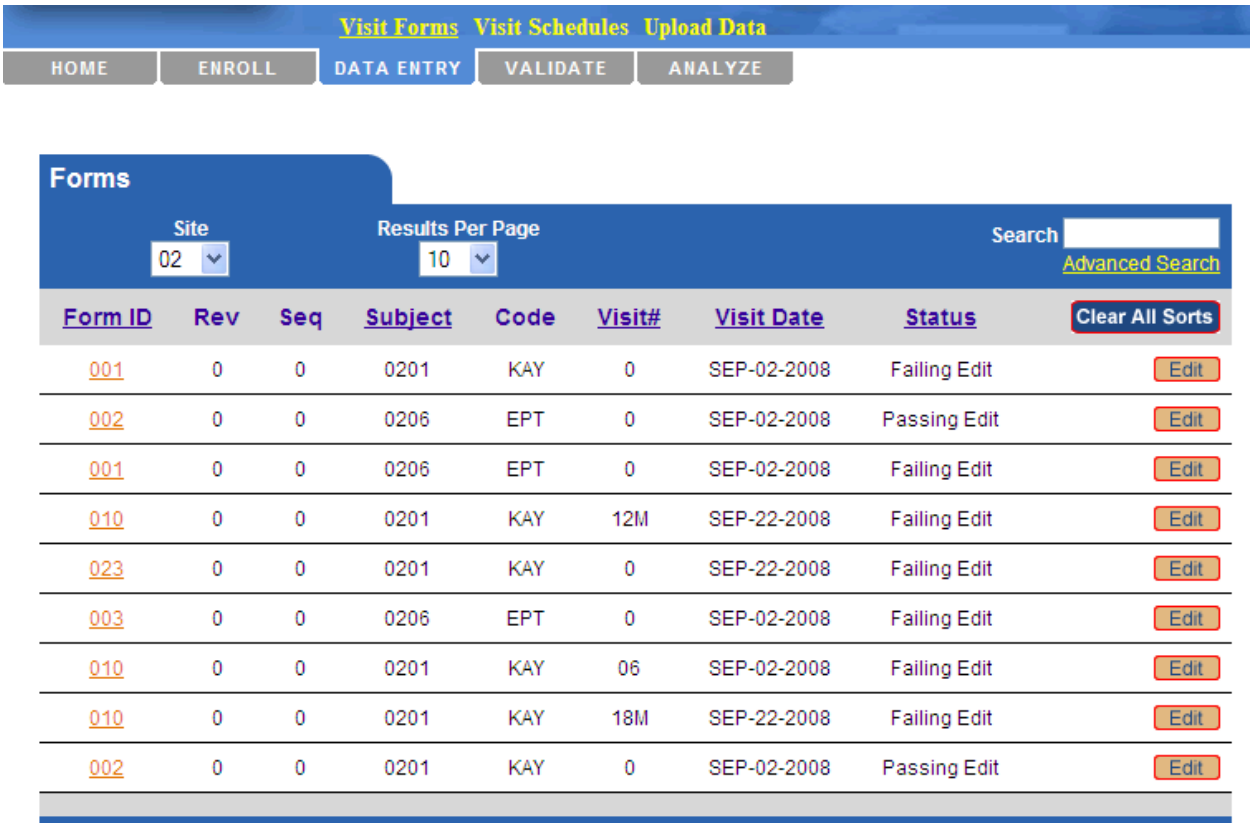
In the event that forms cannot be transmitted due to equipment failure (e.g., the server is down at the DCC or at the Clinical Center) the forms should be keyed as soon as the system becomes available. However, in the event of an SAE, the forms should be faxed to the DCC using the dedicated BABY HUG Follow-up fax line, 443-524-2320, and if fax communication is not possible, the form information should be phoned in to the DCC.

7.1.3 Data Editing

Form edits will be required from time to time. Many data entry fields on the study forms are programmed with a range of acceptable values or responses. Values entered that fall outside of those acceptable ranges will generate an edit report. Also, values that are inconsistent with other values will generate a data edit report (e.g. the answer to one question may be based on the answer to another question). StudyCTMS provides rapid feedback regarding such edits, as queries are generated when the form closes. In reviewing the edit report, it may be necessary to go back to the source document or medical record to see if the value was transcribed correctly or incorrectly into StudyCTMS. Edit reports will also be generated if a required field on a form was left blank. Again, the source document may need to be reviewed to see if the value is available.

7.1.3.1 Corrections Function

StudyCTMS has a corrections function, which allows one to change data that has already been submitted electronically on a study form to the DCC. Users may navigate to the Data Entry page in StudyCTMS to edit existing forms by clicking the 'Edit' button next to the desired form. For example:



Alternatively, users may navigate to the Validate Forms tab and edit those forms that have failed the consistency check edit process.

In some cases even though a human or study range has been validated, the site may wish to correct it. When this occurs, the user should navigate to the field in question and double-click on the exclamation point icon.

Data entry range errors may not be validated as they indicate values that are not possible for database storage in that field. For example, if you attempt to enter a letter into a number field, this will produce a format error.

If, when presented with the Validate Error pop-up, the user clicks the **Validate** button, the pop-up will close, the data point will be stored as "validated" in the database and the exclamation point icon will change from red to yellow  . At any time, if a user decides that the field was validated in error, they simply need to double-click on the yellow icon and choose "Yes" when asked if they want to undo the validation.

7.1.3.2 Editing Data on Archived Documents

If a study form has been pre-printed, all corrections from source documents must also be recorded on the printed study form. Draw a line through the previous response. Write the initials and date next to the previous response. Write in the new response being careful not to obscure the original response.

7.1.4 Storage and Archival

All archived documents, such as paper forms, computer printouts of StudyCTMS forms, corresponding medical records and other source documentation (e.g. WPPSI test booklets) must be signed and dated before they are placed in storage. Archived documents must be stored with other confidential patient files in a locked cabinet or file drawer. Each BABY HUG Follow-up patient should have a set of files organized in such a fashion that any particular document can be easily located and retrieved. Because data entry is performed at the Clinical Centers, which are remote from the DCC, data quality assurance will be derived from site visits that will include audits of the data against the medical record. The DCC may periodically check the quality of the Clinical Center data entry by requesting copies of the original forms for independent data entry and comparison. It therefore becomes critical to store patient files in an orderly fashion to facilitate easy retrieval.

7.2 CENTRAL READER DATA

The Clinical Centers send to the Data Coordinating Center (DCC) all liver/spleen scan, TCD and abdominal sonogram films for central reading. The DCC will log receipt of the films and forward the films and a grading form to the appropriate readers.

Additionally, the Clinical Centers fax to the DCC the following reports: MRI, MRA, CT, TCD and Neuropsychology accompanied by the *Imaging and Neuropsych Reports Transmittal List* fax Form 105. Please see Exhibit 7-1.

7.2.1 Liver/Spleen Scans

The DCC will send the liver/spleen scan films and a blank Form 31 (Liver-Spleen Scan Central Reading) to the first central reader who will assess and grade the films for uptake in the spleen compared to that in the liver. The reviewer will complete Parts II-III of the form, and return the study form and films to the DCC. The DCC coordinator will log receipt of the films, and forward the films with a blank Form 31 to the second reader who will return the films and form to the DCC. If the two gradings disagree, the DCC coordinator will send the films and a blank study form to a third reviewer. The DCC coordinator will complete the remaining sections of the study forms and use StudyCTMS to enter and edit (if necessary) the data on the study forms. The original forms (the study index forms) and the films will be stored in a locked location at the DCC.

7.2.2 Abdominal Sonogram

The DCC will send the abdominal sonogram films and a blank Form 33 (Abdominal Sonogram Central Reading) to the central reader who will grade the films for splenic and renal volume, and assess the gallbladder and biliary system. The reviewer will complete Parts II-III of the form and return the study form and films to the DCC. The DCC coordinator will log receipt of the films, complete the remaining sections of the form and data-enter the form. The DCC coordinator will use StudyCTMS to enter and edit (if necessary) the data on the study form. The original form (the study index form) and the films will be stored in a locked location at the DCC.

7.3 CORE LABORATORY DATA

The Clinical Centers send all blood and urine specimens directly to the appropriate Core Laboratory. All Core Laboratories (Hematology, Biochemistry, Pitted Cell Count, VDJ, HJB, and Cystatin-C) will send data via StudyCTMS .

BABY HUG FOLLOW-UP STUDY

IMAGING AND NEUROPSYCH REPORTS TRANSMITTAL LIST

PART I: IDENTIFYING INFORMATION

1. Patient's ID Number: | | | | | 2. Current Clinic: | | |

3. Patient's Letter Code: | | | |

4. Today's Date: | | | | - | | | - | | | | | (Month - Day - Year)

Print this transmittal form and fax it to the Data Coordinating Center with up to 4 accompanying reports. Check the type of report(s) below.

PART II: TRANSMITTAL INFORMATION

		Check one report per row.				
Test Date	**Report Date**	**MRI**	**MRA**	**CT**	**TCD**	**Neuropsych**
__ __ __-__ __-__ __ __ __	__ __ __-__ __-__ __ __ __					
__ __ __-__ __-__ __ __ __	__ __ __-__ __-__ __ __ __					
__ __ __-__ __-__ __ __ __	__ __ __-__ __-__ __ __ __					
__ __ __-__ __-__ __ __ __	__ __ __-__ __-__ __ __ __					

Comments: _____

_____

Fax this transmittal form and reports to:

BABY HUG Coordinator
BABY HUG Data Coordinating Center

Fax number: (443) 524-2320

Clinical Center staff member completing form and verifying reports:

Name: _____ Certification number: | | | - | | |

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
BABY HUG FOLLOW-UP STUDY
MANUAL OF OPERATIONS

CHAPTER 8

TRAINING AND CERTIFICATION

8.1 INTRODUCTION

In multi-center studies, procedures must be standardized within each Clinical Center and among the participating Clinical Centers to assure that findings from all centers are comparable and, therefore, can be pooled. Certification of Clinical Centers and their staff indicates that they have been instructed in the collection of study data. Specifically, each Clinical Center participating in the BABY HUG Follow-up Study must be certified to enroll and collect data from patients. Staff who will be responsible for enrolling patients, completing data collection forms, performing data entry, collecting specimens and/or sending study specimens to Core Laboratories must be certified. This chapter specifies the requirements for certification of Clinical Centers and their personnel and the responsibilities of the Data Coordinating Center (DCC) for coordinating the certification program.

8.2 TRAINING

Training for the BABY HUG Follow-up Study is organized by the DCC. Training sessions for form data entry will be conducted via the internet using WebEx. Additional training and discussions will be held during Coordinator conference calls and Steering Committee Meetings.

8.3 CLINICAL CENTER CERTIFICATION

In order for a BABY HUG Follow-up Study Clinical Center to be certified to enroll patients and collect specimens and study data, the following requirements must be met:

1. Approval by the NHLBI Project Officer and OSMB Chair of the Clinical Center consent form.
2. Documentation of approval by local Institutional Review Board (IRB) of the BABY

HUG Follow-up Study Protocol and Consent Form, by submission of copies of approvals to the DCC. A copy of the IRB-approved Consent Form must be sent to the DCC each time it is revised. Notification of annual IRB approval is also required.

3. Approval by local institution of a Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule Authorization form.

4. Certification of at least one individual in each of the following staff categories: Principal Investigator and Clinic Coordinator.

Personnel who were certified in the BABY HUG Treatment Study will be able to transfer their certification with some modification. The certification requirements for the BABY HUG Treatment Study can be reviewed in Chapter 11 of the BABY HUG Manual of Operations.

8.4 BABY HUG FOLLOW-UP CERTIFICATION OF CLINICAL CENTER PERSONNEL

The BABY HUG Follow-up Study requires that the following individuals be certified:

- Principal Investigator
- Co-Investigator (if applicable)
- Clinic Coordinator
- Data Manager (if applicable)

8.4.1 Principal Investigator

8.4.1.1 BABY HUG Certified

If the Principal Investigator was previously certified for the BABY HUG Treatment Study, his/her certification can be transferred to the BABY HUG Follow-up Study except he/she needs to complete an updated Conflict of Interest Statement, Form 110 (Exhibit 8-1).

8.4.1.2 Non-BABY HUG Certified

If a new, non-BABY HUG certified Principal Investigator joins the BABY HUG Follow-up Study, he/she must meet the following requirements:

1. Trained by a certified Principal Investigator or by the DCC.

2. Successful completion of the BABY HUG Follow-up Study general knowledge test (see Exhibit 8-2).
3. Submit a Request for Principal Investigator Certification, Form 113 (see Exhibit 8-3).
4. Submission of Conflict of Interest statement, Form 110 (Exhibit 8-1).
5. Human subjects training completed and certificate provided to the DCC.

8.4.2 Co-Investigator (if applicable)

8.4.2.1 BABY HUG Certified

If the Co-Investigator was previously certified for the BABY HUG Treatment Study, his/her certification can be transferred to the BABY HUG Follow-up Study except he/she needs to complete an updated Conflict of Interest Statement, Form 110 (Exhibit 8-1).

8.4.2.2 Non-BABY HUG Certified

If a new, non-BABY HUG certified Co-Investigator joins the BABY HUG Follow-up Study, he/she must meet the following requirements:

1. Trained by a certified Principal Investigator or by the DCC.
2. Successful completion of the BABY HUG Follow-up Study general knowledge test (see Exhibit 8-2).
3. Submit a Request for Co-Investigator Certification, Form 111 (Exhibit 8-3).
4. Submission of Conflict of Interest statement, Form 110 (Exhibit 8-1).
5. Human subjects training completed and certificate provided to the DCC.

8.4.3 Clinic Coordinator

8.4.3.1 BABY HUG Certified

If the Clinic Coordinator was previously certified for the BABY HUG Treatment Study, his/her certification can be transferred to the BABY HUG Follow-up Study except he/she needs to complete an updated Conflict of Interest Statement, Form 110 (Exhibit 8-1).

8.4.3.2 Non-BABY HUG Certified

If a new, non-BABY HUG certified Clinic Coordinator joins the BABY HUG Follow-up Study, he/she must meet the following requirements:

1. Trained by a certified Clinic Coordinator or the DCC.
2. Successful completion of the BABY HUG Follow-up Study general knowledge test (see Exhibit 8-2).
3. Submission of a completed BABY HUG Follow-up Study website individual application (see Exhibit 8-4). Once the website application is received by the DCC, the DCC Coordinator will provide the new Coordinator with a website username and password.
4. Successful completion and data entry of BABY HUG Follow-up Study Forms 01 (Enrollment Form) and 11 (48 Month Visit) for a standard set of patient information (see Exhibit 8-5).
5. Submit a Request for Clinic Coordinator/Data Manager Certification, Form 114 (see Exhibit 8-6).
6. Submission of Conflict of Interest statement, Form 110 (Exhibit 8-1).
7. Human subjects training completed and certificate provided to the DCC.

8.4.4 Data Manager (if applicable)

8.4.4.1 BABY HUG Certified

If the Data Manager was previously certified for the BABY HUG Treatment Study, his/her certification can be transferred to the BABY HUG Follow-up Study except he/she needs to complete an updated Conflict of Interest Statement, Form 110 (Exhibit 8-1).

8.4.4.2 Non-BABY HUG Certified

If a new, non-BABY HUG certified Data Manager joins the BABY HUG Follow-up Study, he/she must meet the following requirements:

1. Trained by a certified Clinic Coordinator or the DCC.

2. Successful completion of the BABY HUG Follow-up Study general knowledge test (see Exhibit 8-2).
3. Submission of a completed BABY HUG Follow-up Study website individual application (see Exhibit 8-4). Once the website application is received by the DCC, the DCC Coordinator will provide the new Data Manager with a website username and password.
4. Successful completion and data entry of BABY HUG Follow-up Study Forms 01 (Enrollment Form) and 11 (48 Month Visit) for a standard set of patient information (see Exhibit 8-5).
5. Submit a Request for Clinic Coordinator/Data Manager Certification, Form 114 (see Exhibit 8-6).
6. Submission of Financial Disclosure, Form 110 (Exhibit 8-1).
7. Human subjects training completed and certificate provided to the DCC.

8.5 ROLE OF THE DATA COORDINATING CENTER IN CERTIFICATION

The tasks related to the certification program for which the DCC staff has responsibility for are:

a. Documentation of certification procedures,
b. Coordination of, participation in, and instruction in training sessions,
c. Distribution, receipt and review of certification materials,
d. Documentation of the completion status of certification requirements for Clinical Centers and Clinical Center staff,
e. Certification of Clinical Centers and Clinical Center staff, and
f. Issue certification numbers to Clinical Center staff.

8.5.1 Processing Requests for Certification of Clinical Center Staff

An individual at the DCC processes all requests for certification. Upon receipt of a request for certification, the DCC reviews the materials in the certification file maintained for

each Clinical Center to assure that all required materials have been received. Requests for certification are then reviewed by designated DCC staff.

8.5.2 Certification of Clinical Center Staff

DCC staff is responsible for review of certification materials submitted for Clinical Center staff.

8.5.3 Notification of Certification

After review of submitted materials, if certification is recommended, the DCC will assign a unique BABY HUG Follow-up Study staff number to the individual. Individuals transferring their BABY HUG Treatment study certification to the BABY HUG Follow-up Study will maintain their existing certification number. An updated listing of Clinical Center Certification Numbers, Form 111 (see Exhibit 8-7) will be sent to the Clinical Center with the new (or transferred) certification number listed next to the individual's name as personnel are certified during the BABY HUG Follow-up Study.

8.5.4 Processing Requests for Certification of Clinical Centers

Requests for Clinical Center certification are also logged at the DCC and each is reviewed to assure that the required staff has been certified and that all requirements have been met. The DCC notifies each Clinical Center of certification to begin patient enrollment by forwarding a completed copy of BABY HUG Follow-up Study Form 112, Notification of Clinical Center Certification (Exhibit 8-8).

8.5.5 Liaison Activities

The Certification Coordinator maintains regular telephone communications with staff in each Clinical Center to detect and help to resolve any problems encountered in the certification process. Problems which the DCC is unable to resolve are referred to the Operations Committee.

8.6 REVIEWING CLINIC COORDINATOR CERTIFICATION

If a Clinic Coordinator fails to meet the standards necessary for conduct of the BABY HUG Follow-up Study, the DCC staff will review the problem(s) with the Steering Committee with a request to the Chairman that the Principal Investigator be contacted to review the problem(s) and solicit any explanation(s). If the DCC staff document no improvement within two months of the date the problem is reviewed by the Steering Committee Chairman with the Principal Investigator, the DCC staff will notify the appropriate individual in writing that his/her certification has been suspended, and other Clinical Center staff will be responsible for the integrity of the performance of the tasks of that coordinator. Copies of this letter will be sent to the Principal Investigator and the Steering Committee. A staff member who has had certification suspended will be re-certified when all of the following conditions have been met: (1) at least 5 forms or one year's work have been reviewed and co-signed by the Principal Investigator and all are satisfactory, (2) any outstanding edit messages and memoranda responses have been received and are satisfactory, and (3) current work is satisfactory and is submitted in a timely fashion.

In the extenuating circumstance when no certified Clinic Coordinator is available at the Clinical Center due to illness or other unexpected events or while new staff are being recruited and certified, BABY HUG Follow-up Study forms will be accepted by the DCC if each form is reviewed and co-signed by the Principal Investigator.

EXHIBIT 8–1
BABY HUG FOLLOW-UP STUDY
FINANCIAL DISCLOSURE

I, the undersigned, certify that:

1. As of _____, neither I, nor my spouse or dependent children own or will buy or trade stock or stock options in any of the companies* providing medication, equipment or financial support in the trial. In addition, I do not have a retainer-type consultant position with any of the companies.*

2. I agree to disclose financial interests as outlined in the BABY HUG Follow-up Study Policy on Conflict-of-Interest during my participation in the BABY HUG Follow-up Study.

If response is no to questions 1 or 2, an explanatory letter is required.

_____ _____
Typed or Printed Name Signature

_____
Date

*Companies include: Bristol-Myers Squibb

EXHIBIT 8-2

BABY HUG FOLLOW-UP STUDY CERTIFICATION TEST

1. Which children are eligible for the BABY HUG Follow-up Study?
   a. BABY HUG patients who were on hydroxyurea
   b. All BABY HUG patients
   c. All BABY HUG patients with at least 18 months of follow-up
   d. Any 2-3 year old child with sickle cell disease at your Clinical Center who is on hydroxyurea

2. Will BABY HUG patients be required to sign a new consent to participate in the BABY HUG Follow-up Study?
   a. Yes
   b. No

3. The BABY HUG Follow-up Study will follow patients until:
   a. June 2009
   b. December 2009
   c. January 2010
   d. June 2011
   e. December 2011

4. Is a BABY HUG patient that has been placed on chronic transfusion eligible for the BABY HUG Follow-up Study?
   a. Yes
   b. No

5. The BABY HUG Follow-up Study is divided into two arms. What are they? (select two)
   a. Hydroxyurea
   b. Placebo
   c. Active
   d. Passive

6. All BABY HUG patients are required to sign up for the BABY HUG Follow-up Study.
   a. True
   b. False

7. The primary objective of the BABY HUG Follow-up Study is:
   a. To assure that all patients are given the same formulation of hydroxyurea.
   b. To monitor the continued safety of hydroxyurea.
   c. To compare reactions to hydroxyurea and placebo.

8. How frequently will patient data be abstracted in the first three years of the BABY HUG Follow-up Study?
   a. Every 2 weeks
   b. Once a month
   c. Every 6 months
   d. Once a year
   e. Every other year

EXHIBIT 8-2 (Continued)

BABY HUG FOLLOW-UP STUDY CERTIFICATION TEST

9. How frequently will patient data be abstracted after three years of the BABY HUG Follow-up Study?
   a. Once a month
   b. Every 6 months
   c. Once a year
   d. Every other year

10. If a child withdrew from BABY HUG, is the child eligible for the BABY HUG Follow-up Study?
   a. No
   b. Yes, if they had at least 18 months of follow-up in BABY HUG.
   c. Yes, regardless of the amount of follow-up in BABY HUG.

_____
NAME

_____ _____
SIGNATURE DATE

EXHIBIT 8-3
BABY HUG FOLLOW-UP STUDY

REQUEST FOR INVESTIGATOR/CO-INVESTIGATOR CERTIFICATION

Clinical Center: _____ Clinical Center No.: ☐☐

Certification as BABY HUG Follow-up Study Co-Investigator is requested for:

Name _____

The individual named above has (all MUST be checked):

* ☐ Successfully completed the BABY HUG Follow-up Study general knowledge test.

☐ (*Co-Principal Investigators only*) attended a BABY HUG Follow-up Study training session on _____ (Date(s)) or received training from _____ (Name) who is a fully certified BABY HUG Follow-up Study Principal Investigator

*To be submitted with this form if not previously submitted.

Principal Investigator: _____
Signature

Date: _____

EXHIBIT 8-4

BABY HUG FOLLOW-UP STUDY
USER APPLICATION

Complete one form per user.
Please type or print clearly.
FAX to C-TASC (443) 524-2320

Date: _____

Site Number/Name: _____

User Name: _____

User e-mail: _____

User Phone Number: area code ( ) _____

Computer / Operating System: _____

Browser / Version: _____

Certification Requested: (Select One)

☐ Content Only: The user may browse web site content such as manuals and forms, but may not enter, modify or view data.

☐ Data Entry and Content: The user may browse web site content such as manuals and forms, and may enter, modify and view data.

For Computer Services Use Only!

		Comments:
Test IDs:	_____	
Passed Comparison:	_____	_____
Date Certified:	_____	_____
Completed by:	_____	_____
USER LOGON Assigned:	_____	_____
USER PASSWORD Assigned:	_____	_____
USER NUMBER Assigned:	_____	_____

EXHIBIT 8-5

Sample Patient Narrative
Practice Data for Forms 01 and 11

For the practice forms, a "dummy" patient ID will need to be used so that the system will not confuse the practice test with real data. Therefore, please use the following convention when writing patient IDs in your test forms:

The patient ID has 4 digits. The first will always be a "9". The second and third digits will be your Clinical Center number. The fourth digit will be 0-9, with the first person from your Clinical Center who is filling out the test forms using 0, the second person using 1 and so on. Please keep track of which fourth digit you are on at your own Clinical Center.

For example, if we had a Clinical Center 15, the patient ID would be: 9150 for the first forms test. It would be 9151 for the second forms test and so on.

Please replace the "XXXX" wherever patient ID is mentioned below with this convention for your Clinical Center.

At the end of the forms, use the dummy certification number 99-99.

Medical Record Date: August 14, 2008

Patient XXXX from Clinic 99 with Patient Letter Code XYZ was seen in the clinic today and signed consent for the BABY HUG Follow-up Study. At the time of consent, the family agreed to have their child's information included in the data file and they agreed to have their child's blood specimens saved indefinitely so that it could be used for future research on sickle cell disease and related disorders. The family agreed to have their child participate in the active arm of the BABY HUG Follow-up Study which means they will return after 24 months of follow-up to have some or all of the 24 month studies performed.

Patient XXXX was given a script for 246 mg of hydroxyurea and mom was instructed to take it to the hospital pharmacy to be filled.

Medical Record Date: December 12, 2008

Patient XXXX from Clinic 99 with Patient Letter Code XYZ returns to clinic today to have BABY HUG Follow-up Study exit studies performed. A urine specimen was collected, labeled with label number 99998 and shipped to the Georgia Health Sciences University for processing. 5 ml of blood was drawn, labeled with label number 99975 and shipped to the Georgia Health Sciences University for processing. There was insufficient blood available to send specimens to the remaining BABY HUG Follow-up Study core laboratories. The family agreed to return on December 19, 2008 to have the remaining specimens collected.

Medical Record Date: December 19, 2008

Patient XXXX from Clinic 99 with Patient Letter Code XYZ returns to clinic today to have the remaining required blood specimens collected. 3 ml of blood was collected in a lavender top tube, labeled with label number 99964 and shipped to St. Jude for VDJ/HJB processing. 0.1 ml of blood was collected, labeled with label number 99983 and shipped to UTSW for processing. 0.5 ml of blood was collected in a red top tube, labeled with label number 99970 and shipped to St. Jude for processing, along with the VDJ specimen. 0.5 ml of blood was collected in a red top tube, labeled with label number 99989 and shipped to the George Health Sciences University for processing. Patient XXXX has completed all of his BABY HUG Follow-up Study exit procedures.

EXHIBIT 8-6
BABY HUG FOLLOW-UP STUDY

REQUEST FOR CLINIC COORDINATOR/DATA MANAGER CERTIFICATION

Clinical Center: _____ Clinical Center No.: | | |

Certification as BABY HUG Follow-up Study Clinic Coordinator is requested for:

Name _____

The individual named above has (all MUST be checked):

* ☐ Attended a BABY HUG Follow-up Study Training Session on _____ Dates(s)

OR

☐ Received equivalent training at a Clinical Center by: _____ Name

who is a fully certified BABY HUG Follow-up Study Clinic Coordinator.

* ☐ Successfully completed the BABY HUG Follow-up Study general knowledge test.

* ☐ Completed a BABY HUG Follow-up Study website individual application.

* ☐ Successfully completed and data entered BABY HUG Follow-up Study Forms 01 and 11 for the standard patient narrative, and submitted the form printouts to the DCC.

*To be submitted with this form if not previously submitted.

Principal Investigator: _____ Signature

Date: _____

EXHIBIT 8-7
BABY HUG FOLLOW-UP STUDY

CLINICAL CENTER CERTIFICATION NUMBERS

Clinical Center: _____ Clinical Center No.: | | |

Name	Certification No.	Position
_____		- 0 1	Principal Investigator
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____
_____		-	_____

Issued by: _____
DCC Staff Member

Date: _____

EXHIBIT 8-8
BABY HUG FOLLOW-UP STUDY

NOTIFICATION OF CLINICAL CENTER CERTIFICATION

Clinical Center: _____ Clinical Center No.: | | |

Principal Investigator: _____

YOUR CLINICAL CENTER HAS BEEN CERTIFIED TO BEGIN CONSENTING PATIENTS FOR THE BABY HUG FOLLOW-UP STUDY.

Approved by: _____

Date: _____

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
BABY HUG FOLLOW-UP STUDY
MANUAL OF OPERATIONS

CHAPTER 9

STUDY MONITORING AND REPORTING RESULTS

9.1 INTRODUCTION

Monitoring will occur on an as needed basis and will be conducted by the OSMB and Steering Committee.

9.2 MONITORING FOR TOXICITY: 2 MONTHS POST-BABY HUG TREATMENT STUDY

9.2.1 Lab Review for Enrollments Within Two Months of BABY HUG Study

Blood count review for tests within 2 months of exit from the BABY HUG Treatment Study Complete blood count (CBC) data from visits within 2 months of completion of randomized treatment on the BABY HUG Treatment Study should not be viewed by PI or Nurse Coordinator staff who were blinded during the treatment study. After two months have passed from completion of the treatment study, local study staff no longer need to be blinded to results of the CBC.

9.2.2 Lab Review for Enrollments After Two Months Post-BABY HUG Study

Children enrolled in the follow-up study who are more than two months post-completion of the BABY HUG Treatment Study have no restriction on who may view their lab results.

9.3 MONITORING FOR ADVERSE EVENTS

Clinical events (hospitalizations and specific other sickle cell related events) will be retrospectively abstracted from the medical records of study participants at specified intervals (two times per year for the first three years, annually thereafter). Clinical Centers will be asked to classify the event based upon BABY HUG criteria using simple yes/no data forms. Definitions

of clinical events can be found in Appendix F of the BABY HUG Treatment Study Protocol except for the post-hoc Steering Committee definition of splenic sequestration which is defined as follows:

Splenic Sequestration: 2 cm or more increase from last visit in palpable spleen size AND a decrease in Hb of 2 g/dL or more below the 3-month rolling average.

For children who agree to active Follow-up, standard clinical trial prospective, severe adverse event (SAE) reporting for the items listed in Chapter 3, Section 3.4.2.1 pages 4-5 of this Manual of Operations must be captured for the five days following completion of each of the active studies using BABY HUG Follow-up Study Form 25 (Serious Adverse Event) and must be submitted to C-TASC using a MedWatch. See Chapter 3.

9.4 MONITORING DATA QUALITY

The web-based Clinical Trial Management System (StudyCTMS) monitors for data errors (e.g., when an end user types “MAT” instead of “MAY”) at the time of data entry. StudyCTMS also edits forms entered at the time of data entry. These edits give instant feedback to Clinical Center staff on missing items, inconsistent items and items out of “normal” range.

9.5 MONITORING SPECIMEN AND FILM QUALITY

On a continual basis, all specimens received in the Core Laboratories are inspected on arrival including labeling with comparison to transmittal lists in the shipments. Inconsistencies in labeling and problems with specimen condition (e.g., cracked tubes, clotted CBC specimens, insufficient quantities) are communicated to the Clinical Center staff within 24 hours of report to the DCC. Laboratory results are checked for validity prior to entry in the follow-up study database. The core laboratory is queried regarding out-of-range results.

Liver-spleen scan and abdominal sonogram films are examined for adequacy by the central readers. Films judged to be inadequate for reading are returned to the Clinical Center

for reprocessing. Within 10 days of receipt, the films should be reprocessed and sent back to the DCC.

9.6 INSTITUTIONAL DATA AND SAFETY MONITORING AND REPORTING

Accrual and safety data will be under continual review by the DCC, NHLBI and NICHD.

Accrual and safety data will also be reviewed annually by each Clinical Center's IRB. Prior to implementation of this study, the Protocol and the proposed patient consent forms will be reviewed and approved by the local IRB. This committee will also approve all amendments to the Protocol or informed consent, and conduct continuing annual review so long as the BABY HUG Follow-up Study is open.

Every six months, data is retroactively abstracted for review by treatment group by the OSMB. A report will be forwarded to the OSMB at these times and their recommendations will be expeditiously implemented. The OSMB reserves the right to recommend early termination of the study for considerations of safety or efficacy.

9.7 CLINICAL CENTER MONITORING

9.7.1 Protocol Deviations

DCC staff are responsible for monitoring for protocol deviations and for notifying all appropriate BABY HUG Follow-up Study personnel or appropriate committees of any deviations when the DCC becomes aware of them (e.g., performing special studies outside of the BABY HUG Follow-up window). If a clinical center discovers a protocol deviation, email one of the BABY HUG Follow-Up staff at the DCC with the information (bfish@c-tasc.com).

9.7.2 Performance Reports

Performance reports are prepared by the DCC staff and distributed to the Clinical Centers semi-annually. These reports include information on forms entered, edited and printed, special study procedures performed, laboratory specimens collected, and protocol deviations.

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL

BABY HUG FOLLOW-UP STUDY
MANUAL OF OPERATIONS

CHAPTER 10

DATA COORDINATING CENTER RESPONSIBILITIES

10.1 INTRODUCTION

The Data Coordinating Center (DCC) is organized and staffed as part of Clinical Trials & Surveys Corp. (C-TASC) to serve the needs of the BABY HUG Follow-up Study. The DCC staff fulfill key roles in developing and implementing the study's statistical design, data collection and management, and analysis of study results. The major responsibilities of the DCC, which serves as the central data repository for the information collected under the common study protocol, are:

(1) serve as communication center for the study;

(2) provide the Internet data entry system for all study data;

(3) maintain a central database of data integrated from all Clinical Centers, Core Laboratories and central reviewers; and

(4) generate analyses to monitor for evidence of adverse effects, safety monitoring and adherence to the study protocol. The objectives and procedures designed to achieve these obligations are presented in this chapter.

10.2 OBJECTIVES OF THE DATA COORDINATING CENTER

The general aims of the BABY HUG Follow-up Study DCC are to:

- Serve as a collaborating partner with the other Investigators in the organization, design, conduct, and analysis of the study.
- Provide biostatistical expertise to the study in the area of design and operation of this multicenter study.
- Work with the other Investigators and consultants to draft and revise as necessary the Protocol, Manual of Operations, and study forms.

- Assist the NHLBI in maintaining an Investigational New Drug (IND) application with the FDA for hydroxyurea usage in young children.
- Provide expertise in the area of Internet data entry and statistical analysis.
- Develop and implement the required data processing procedures for handling all study forms, core laboratory results and other materials.
- Develop, implement and maintain quality control procedures to detect and correct deficiencies in data collection, processing or analyses.
- Provide facilities and staff to carry out appropriate analyses to monitor the study for evidence of adverse effects.
- Establish and maintain subcontracts with Core Laboratories and medical consultants as needed by the study.
- Serve as the communication center for the study.
- Prepare progress reports and assist in preparation of publications.

10.3 PLANNING, TRAINING AND MEETING SUPPORT

The members of the BABY HUG Follow-up Study DCC play a major role in the organization and conduct of Investigator meetings, subcommittee meetings, and conference calls held during all phases of the study. The BABY HUG Follow-up Study DCC staff provide training to the BABY HUG Follow-up Study Clinical Center staff in the collection and processing of data, as necessary. In addition, the BABY HUG Follow-up Study DCC staff provide logistical support for orientation and training sessions.

10.4 STUDY DOCUMENTS AND SUPPLIES

DCC staff are responsible for the coordination of the preparation of the Protocol and Manual of Operations. DCC staff and the Principal Investigators will collaborate in the development and finalization of these documents. DCC staff will periodically review current procedures and develop additional procedures as needed throughout the course of the study. The DCC will update the Protocol and Manual of Operations as study policies and procedures

are added, deleted or changed. Updated revisions will be provided to all Clinical Centers and Core Laboratories.

The DCC staff prepare all the BABY HUG Follow-up Study forms and corresponding QxQ's. All forms changes will also be prepared by the DCC.

DCC staff will assist the National Heart, Lung, and Blood Institute staff in maintaining the Investigational New Drug (IND) application to the Federal Drug Agency (FDA) for hydroxyurea in this age group of children.

DCC supplies each Clinical Center with study notebooks containing the Protocol, Manual of Operations, Forms and QxQ's, and Address Directory. Updates will be sent as needed; the DCC posts the most recent version of these documents on the BABY HUG Follow-up Study website. (See Chapter 14 for information on the website.)

The DCC staff prepare and supply all BABY HUG Follow-up Study customized supplies (e.g. patient specimen and film labels, FedEx preprinted shipping labels, etc.). The DCC also provides the Clinical Centers with neuropsychological testing booklets, sample notebooks for filing patient study documentation and materials, and contact information cards.

10.5 CLINICAL CENTER COMMUNICATIONS

The DCC serves as the communication center for the study.

The DCC staff are a resource for the numerous telephone inquires and written inquiries concerning the study procedures from study Investigators and Clinical Center personnel.

The DCC issues numbered memoranda to Principal Investigators and/or coordinators to impart study-wide policies, procedures, announcements, operational issues, etc., and to request information.

The DCC staff provide logistical support for meetings, conference calls and training sessions. They are responsible for preparing handouts and other materials for meeting participants as well as for preparing and distributing the minutes of these meetings.

DCC staff maintain and distribute a BABY HUG Follow-up Study Address Directory. This directory contains a listing of study personnel from each Clinical Center, each Core Laboratory, all study Consultants, as well as personnel from the Program Offices at the NHLBI and NICHD and the Data Coordinating Center. This directory is updated periodically and posted to the study website.

Protocol exceptions for eligible patients will be considered by the Operations Committee and may be granted as long as study integrity is not compromised. If the committee arrives at a recommendation to grant an exception to the Protocol, the local IRB will be notified and the exception will be conducted in accordance with the local IRB's Standard Operating Procedures.

10.6 DATA COLLECTION AND STORAGE

The BABY HUG Follow-up Study Manual of Operations provides a description of study design, organization, methods, definitions, and procedures used in data collection. The DCC staff in conjunction with appropriate BABY HUG Follow-up Study Investigators coordinate the preparation of this document.

10.6.1 Data from the Clinical Centers

The DCC programming staff are responsible for developing an Internet data entry system. (See Chapter 7 for a description of the Web-based Study Clinical Trial Management System [StudyCTMS].) Clinical Center staff submit data from study visits and data abstractions into the BABY HUG Follow-up Study database via StudyCTMS. Data must be entered into the database within specified time frames before being declared delinquent or missing. (See Chapter 7 on Data Entry.)

10.6.2 Data from the Core Laboratories

Specimens are sent directly to the Hematology, Biochemistry, Pitted Cell, VDJ and Cystatin-C Core Laboratories from the Clinical Centers. Specimen transmittal information is contained in forms entered into the BABY HUG Follow-up Study database via StudyCTMS. All Core Laboratory data are transmitted electronically to the DCC. The DCC programming staff

are responsible for developing and implementing the procedures to receive and store the data from the Core Laboratories. A regular schedule for transmission of these data is established.

10.6.3 Data from Central Readers

All film images and CDs are sent to the Data Coordinating Center from the Clinical Centers, and film and CD transmittal information is contained in forms entered into the BABY HUG Follow-up Study database via StudyCTMS. DCC staff send the films and CDs to the respective central readers who complete the appropriate reading form, send the form and the films back to the DCC. DCC staff enter the data into the BABY HUG Follow-up Study database via StudyCTMS. The films are stored in a secure location at the DCC.

10.6.4 Storage System for Study Documents

All important study documents are posted on the BABY HUG Follow-up Study website which is updated regularly. This includes study reports, minutes of meetings and conference calls, numbered memos, Forms and QxQs, the Protocol, and the Manual of Operations.

10.7 DATA MANAGEMENT AND MAINTENANCE

The DCC data management staff have designed and implemented the Internet data entry system, StudyCTMS, to be used in the Clinical Centers. The Clinical Center staff are responsible for data entry, data editing, and corrections, if necessary, of all study forms. These procedures are described in Chapter 7. The DCC staff are responsible for storing and analyzing all received study data.

10.7.1 Form Data

Forms are edited for acceptable codes, valid ranges and logical consistency by electronic checks during data entry at the Clinical Center. A form is submitted to the DCC upon clicking the submit button in the form application. All ranges and logical consistency checks are executed upon submit.

All corrections made are electronically audited. The audit file includes the old and new values for the field, date of the correction and who made the correction. The form is

automatically marked as corrected as soon as responses to edits have been made and accepted.

10.7.2 Core Laboratory Results

Results from core laboratories are checked for acceptable codes and valid ranges. Data outside the ranges are not imported into the database until verified.

10.8 DATA ANALYSES AND REPORTS

Details of the data analysis plan are contained in the BABY HUG Follow-up Study protocol. Monthly reports to the NHLBI and semi-annual reports (or others, as needed) for the Data Safety and Monitoring Board are based on the data.

10.9 DATA PUBLICATION AND REPORTING

DCC staff will assist, if requested, the participating Clinical Center staff in the preparation of publications which have received prior approval according to study procedures (see Chapter 13).

Upon request of the National Institutes of Health (NIH,) any and all of the above data are made available to the NIH to access and utilize at any time after the completion of the BABY HUG Follow-up Study. At that time, any and all data requested by the NIH are transferred to the National Heart, Lung, and Blood Institute (NHLBI).

10.10 PATIENT PRIVACY, CONFIDENTIALITY OF DATA, AND DATA SECURITY

Because of the importance of protecting study data at the DCC from theft or unauthorized perusal or alteration, access to computer files is restricted through the use of assigned individual usernames and passwords. Protection of the computer files from catastrophic loss is accomplished by a backup system.

To maintain patient privacy, the study records submitted to the DCC do not contain participants' names, addresses or other identifying information. Each participant record is identified by a unique four-digit Patient ID Number and a three-character Patient Letter Code.

Names and addresses corresponding to the identifying codes are kept on file at the Clinical Center.

DCC staff utilize a variety of safeguards to protect the study from catastrophic loss of data. The BABY HUG Follow-up Study database is archived on a daily basis. Other files including programs used for all data management functions are fully archived once every week with an "incremental" back-up daily. An incremental back-up is one in which only files that have been modified are archived. The back-up system is designed to permit the restoration of the system with a minimum expenditure of time and money should any file be destroyed by a man-made or natural disaster. To protect the integrity of the servers running study systems, images (a complete copy) of each server is taken weekly and stored on and off site. C-TASC uses Symantec Recovery Server allowing rapid reimplementation of a server even in cases of complete hardware failure.

Copies of analysis files and programs used in the preparation of scientific presentations and publications are retained for the duration of the contract and stored off site. The analysis files include the programs and procedures that are utilized to extract the data from the database.

10.11 QUALITY CONTROL

10.11.1 Certification

The DCC staff has developed, implemented and monitored the BABY HUG Follow-up Study staff certification program outlined in Chapter 8, including specific DCC responsibilities. The DCC staff maintain a roster of certified staff for each Clinical Center.

10.11.2 Quality Assurance of Clinical Center Data

Clinical Center personnel are trained during training sessions or are instructed by a certified staff member on the BABY HUG Follow-up Study StudyCTMS. As part of the certification process, they enter the data for selected forms using a standard patient narrative provided by the DCC. The data records from these forms are compared to the master file at the DCC and discrepancies noted.

10.11.3 Quality Assurance of Information Stored in Computer Database

All forms are extensively edited during data entry. To test edit programs, a mock set of study forms which contain errors and inconsistencies are used. The edit program is also run on a few forms received from the Clinical Centers and the edit output is carefully checked. If that test indicates no problem, the edit program becomes part of the usual maintenance procedure, but the edit output continues to be checked for a period of time before deciding the program has been adequately tested.

10.11.4 Performance Reports

Performance of the Clinical Centers is assessed in reports. These reports include consideration of the following:

1. Number of study forms that have been entered, passed edit and printed.
2. Number of study visits that have been completed during the ideal or extended window. (For the BABY HUG Follow-up Study, this will include the 24 month visit for the active group and the 48 month visit for all other participants.)
3. Number of Data record abstractions completed within each 6 month or 1 year window.

The DCC staff compare performance and quality of submitted materials for items such as forms past due, studies not performed, or labs not collected, etc. among Clinical Centers.

10.11.5 Site (or Audit) Visits

In addition to preparing the Clinical Center performance monitoring reports, the DCC staff ensure data quality by conducting periodic site visits (or audit visits) to the Clinical Centers. The data on patient medical records are compared against listings of data residing on the BABY HUG Follow-up Study database for selected forms as of the date of the request for a site visit. Using the data as of the site visit request should prevent any audit-prompted revisions of the data form(s). Recertification of Clinical Center personnel responsible for key areas of data collection may also be performed during site visits.

Each of the BABY HUG Follow-up Study Clinical Centers will be site visited at least once during the study. The Site Visit Team will include the NHLBI Project Officer and/or other designated staff and DCC staff.

During the site visits, the team will conduct an audit of the accuracy of data reported from the medical record for a random sample of cases. The consent forms will be reviewed. The Clinical Center staff will be notified prior to the visit what information should be available. Differences between the medical record and the database will be brought to the attention of the Clinical Center staff and resolved. The results of the audit (Site Visit Reports) will be submitted to the Principal Investigator of each Clinical Center, and the NHLBI and NICHD Project Officers.

10.11.6 Quality Control of the Data Coordinating Center

DCC staff activities are governed by the C-TASC Standard Operation Procedures (SOP) for the conduct of C-TASC business. A copy of the Table of Contents for the C-TASC SOP is contained in Exhibit 10-1 to insure the quality of the data and analyses.

10.12 DATA COORDINATING CENTER CONTACTS

DCC staff serve as a resource for all BABY HUG Follow-up Study Clinical Center staff and Core Laboratory staff. Questions concerning the Protocol, study procedures, form entry or other study issues may be directed to appropriate DCC staff (Principal Investigator, Study Manager, Coordinator or Data Management staff). Names and telephone numbers of current DCC staff are given in the BABY HUG Follow-up Study Address Directory.

EXHIBIT 10-1

CLINICAL TRIALS & SURVEYS CORP. (C-TASC)

STANDARD OPERATING PROCEDURES

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DATA MANAGEMENT

GENERAL ADMINISTRATION

INTERIM ANALYSIS

INFORMATION TECHNOLOGY

		EFFECTIVE DATE
IT 001	OPERATIONS MANAGEMENT OF DATA CENTER SYSTEMS	10/01/2010
IT 002	C-TASC DATA CENTER AND IT SECURITY	10/01/2010
IT 003	BACK-UP AND RECOVERY	11/01/2010
IT 004	PASSWORD STANDARDS AND MANAGEMENT	12/10/2010
IT 005	INSTALLING, MODIFYING AND REMOVING HARDWARE	11/01/2010
IT 006	INSTALLING, MODIFYING AND REMOVING SOFTWARE	11/01/2010
IT 007	AUTHORIZATION TO PROCESS	11/01/2010

PROJECT MANAGEMENT

		EFFECTIVE DATE
PM 501	COMMUNICATIONS	12/12/2008
PM 502	INVESTIGATIONAL PRODUCT INVENTORY MANAGEMENT	12/12/2008
PM 503	DOCUMENT AND RECORDS RETENTION	12/12/2008
PM 504	ROUTINE MONITORING VISITS	12/12/2008
PM 505	STUDY CLOSEOUT VISIT	12/12/2008
PM 506	ENSURING INVESTIGATOR COMPLIANCE	12/12/2008

PROTOCOL DEVELOPMENT

		EFFECTIVE DATE
PD 302	INVESTIGATOR BROCHURES	11/26/2008
PD 303	INFORMED CONSENT DEVELOPMENT	02/02/2009
PD 304	CASE REPORT FORM DEVELOPMENT	11/26/2008
PD 305	DEVELOPMENT OF QXQ INSTRUCTIONS	11/26/2008
PD 306	MANUAL OF OPERATIONS DEVELOPMENT	11/26/2008

QUALITY ASSURANCE

		EFFECTIVE DATE
QA 001	COMPUTER SYSTEM VALIDATION PACKAGE MANAGEMENT	11/01/2010
QA 002	FORMAL TESTING PRACTICES	11/01/2010
QA 003	INTERNAL AUDITS	12/10/2010
QA 004	HOSTING REGULATORY AGENCY INSPECTIONS	02/07/2011
QA 005	CONDUCTING VENDOR AUDITS	02/07/2011
QA 006	TRAINING AND EDUCATION	03/07/2011
QA 007	DEVIATIONS	02/07/2011

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		EFFECTIVE DATE
RA 201	FDA CONTACTS AND MEETINGS	11/21/2008
RA 202	FDA SUBMISSIONS	11/21/2008
RA 203	FDA REPORTING REQUIREMENTS	11/21/2008
RA 204	GENE TRANSFER RESEARCH	11/21/2008

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		EFFECTIVE DATE
DEV 001	SOFTWARE DEVELOPMENT LIFE CYCLE (SDLC) FOR NEW FEATURES, FUNCTIONALITY, AND ENHANCEMENTS	11/01/2010
DEV 002	SOFTWARE DEVELOPMENT LIFE CYCLE: BUG FIXES	11/01/2010
DEV 003	SOFTWARE DEVELOPMENT CONFIGURATION MANAGEMENT & CODE CONTROL	11/01/2010
DEV 004	SOFTWARE DEVELOPMENT LIFE CYCLE CODE REVIEW	12/10/2010
DEV 005	SOFTWARE DEVELOPMENT CODING STANDARDS – JAVA	12/10/2010
DEV 006	SOFTWARE DEVELOPMENT CODING STANDARDS – ORACLE	12/10/2010
DEV 007	DATA CHANGES	12/10/2010

STATISTICAL

		EFFECTIVE DATE
STAT 1001	ORGANIZATION OF SAS PROGRAMS AND DATA SETS	09/08/2008
STAT 1002	DOCUMENTATION OF SAS PROGRAMS	09/08/2008
STAT 1003	CREATION OF SAS DATA SETS FROM DATA COLLECTION FORMS	09/08/2008
STAT 1004	CREATION OF SAS DATA SETS FROM CORE LABORATORY DATA TRANSFERS	09/08/2008
STAT 1005	CREATION OF SECONDARY SAS DATA SETS	09/08/2008
STAT 1006	HARD CODE CORRECTIONS TO DATA SETS	09/08/2008
STAT 1007	GENERATION OF FREEZE DATA SETS	09/08/2008
STAT 1008	GENERATION OF PERFORMANCE REPORTS	09/08/2008
STAT 1009	GENERATING ANALYSES FOR INVESTIGATORS	09/08/2008
STAT 1010	GENERATING DATA SETS FOR INVESTIGATORS	09/08/2008
STAT 1011	CREATION AND MAINTENANCE OF SHARED SAS MACROS	09/08/2008
STAT 1012	GENERATING DATA SETS FOR ANALYSES	09/08/2008

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		EFFECTIVE DATE
SM 001	STUDY IMPLEMENTATION LIFE CYCLE	01/10/2011
SM 003	STUDY PROTOCOL AND AMENDMENT	04/04/2011

STUDY START-UP

		EFFECTIVE DATE
SS 401	INVESTIGATOR SELECTION AND QUALIFICATION	11/24/2008
SS 402	INITIATION VISIT AND SITE TRAINING	11/24/2008

SUBJECT MANAGEMENT

		EFFECTIVE DATE
SM 601	HUMAN SUBJECT PROTECTION	02/12/2009
SM 602	SUBJECT RECRUITMENT PRACTICES	01/12/2009
SM 603	SUBJECT ELIGIBILITY AND ENROLLMENT	12/12/2008
SM 604	SPECIMEN MANAGEMENT	12/12/2008
SM 605	ADVERSE EVENT RECOGNITION AND REPORTING	02/12/2009
SM 606	PROTECTED HEALTH INFORMATION	01/12/2009

FORMS

		EFFECTIVE DATE
GA FM 001	DOCUMENT CONTROL FORM	04/04/2011
IT FM 001	DATACENTER DAILY OPERATIONS CHECKLIST	10/01/2010
IT FM 002	C-TASC OFF-SITE TAPE STORAGE LOG	11/01/2010
IT FM 003	C-TASC FILE RESTORE LOG	11/01/2010
IT FM 004	RECOVERY DRILL SUMMARY FORM	11/01/2010
IT FM 005	INSTALLING HARDWARE/SOFTWARE CONTENTS AND REVIEW	11/01/2010
IT FM 006	MODIFYING AND REMOVING HARDWARE/SOFTWARE CONTENTS AND REVIEW	11/01/2010
QA FM 001	DEVIATION FORM	02/07/2011

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
BABY HUG FOLLOW-UP STUDY
MANUAL OF OPERATIONS

CHAPTER 11

CLOSE-OUT PROCEDURES

11.1 STUDY END DATE

The common termination date for this study is December 31, 2011.

Because the last child recruited into the BABY HUG Treatment Study will complete the study by September 2009, it is estimated that the treatment study will be completed and results disseminated during the follow-up study. Whether HU is found to be efficacious in the BABY HUG Treatment Study or not, and whether or not toxicities are found in the treatment study, the follow-up study will be performed. If interim or final analysis of the BABY HUG Treatment Study demonstrates that HU is not safe and/or efficacious, parents/guardians with children on the follow-up study will be advised to stop HU treatment if their children are currently receiving HU.

11.2 DATA CLEAN-UP, CLOSURE AND STORAGE

The DCC will perform close-out visits at each Clinical Center to assure that all of the following tasks have been completed:

<u>IRB Approvals</u>

- Review all IRB approvals.
- Verify that all IRB approvals were obtained for all patients.

<u>Consent Forms and Enrollment Records</u>

- Review signed consent forms for all subjects enrolled since the last monitoring visit and compare with the Investigator's enrollment records.
- Review eligibility criteria for all patients.

Study Forms

- CRFs: Collect all remaining CRFs and update any outstanding data correction tabulations.
- Review the site's study files to ensure that all study documentation is current and complete.

Study Materials

- The monitor(s) will discuss with the Clinical Center the disposition of BABY HUG study materials that should be kept at the site and the procedures that must be implemented to closeout the study.

Visit Log

- Make certain all visits by monitors and other authorized personnel have been documented and that the log is complete.

Monitoring Report

- DCC staff will complete the monitoring report and make the final determination that the Investigator's obligations have been met and that all study and regulatory requirements have been fulfilled.

Laboratory

- Verify that all specimens for laboratory studies have been forwarded to the appropriate location(s).

The Clinical Centers will complete the following tasks in preparation for the DCC close-out visit of their site:

IRB Approvals

- The Clinical Center has informed the IRB of the closeout visit and study completion. The Clinical Center has this document ready to show the monitor.

Consent Forms and Enrollment Records

- Make sure the enrollment records are complete and ready for the monitor.

Study Forms

- The Clinical Center has resolved and is ready to provide to the monitor any outstanding DCC data queries from past visits or/and audits.
- Make all remaining corrections to the CRFs.
- The Clinical Center has all forms ready for the monitor to review.

Documentation

- The PI may keep a copy of the Protocol and Manual of Operations or he/she can return it to the DCC. It is recommended that they be retained at the site for any future reference.
- Clinical Center may retain one copy of each unused form. All other copies of forms must be returned to the DCC. The monitor will take these at close out.

Supplies

As applicable:

- Clinical Center staff must destroy all gluteraldehyde tubes.
- Clinical Center staff must destroy all microtainers sent to the Clinical Center for study use.
- Clinical Center staff must return all study label sheets to the DCC.
- Arrange to have remaining study incidentals and accessories/supplies collected and shipped back to C-TASC.

Investigator's Final Report

- The PI must prepare a final report to the project officers and contract officers at the NHLBI and NICHD. The report should include an enrollment summary, information on SAEs, and any other relevant information about the Clinical Center.

- The PI must prepare a final report to the Clinical Center IRB. The report should contain all the information that is in the report to the sponsors, as well as any other information specifically requested by the IRB.
- If applicable, the PI must notify the Clinical Center's Hospital Administration that the BABY HUG study is no longer being conducted at the Clinical Center/hospital.
- Submit the final report to C-TASC within 90 days of the closeout visit.

Storage

- Clinical Center staff must store completed study forms, signed consent forms and all IRB correspondence at the site. Location of materials should be noted in the Clinical Center closeout report. Records must be kept for two years after the NDA is approved for marketing, or if the NDA is not approved, for two years after the study is discontinued and the FDA notified in accordance with ICH GCP.

The DCC will verify in a final site visit report to individual sites that each was properly closed.

11.3 FINAL STUDY DATA AND DISSEMINATION OF RESULTS

The OSMB will review the final data analyses regarding the main findings of the study at a planned final meeting. These data analyses will form the basis of the final consensus recommendations from the OSMB, the Steering Committee and the NHLBI. These consensus recommendations will be shared first with the study children's families and will be made public as soon as possible thereafter. The final data analysis report and any databank studies will be available for submission to the FDA and for archiving.

Public data files will be made available according to NHLBI policy.

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
BABY HUG FOLLOW-UP STUDY
MANUAL OF OPERATIONS

CHAPTER 12

ORGANIZATIONAL STRUCTURE AND PARTICIPATING UNITS

12.1 INTRODUCTION

The BABY HUG Follow-up Study will be conducted in fourteen Clinical Centers, a Data Coordinating Center and Core Laboratories. The Clinical Center staff will be trained in accordance with the procedures set out in this Manual of Operations. The objective is to standardize all study procedures carried out in the Clinical Centers and at the operational central units.

Study monitoring will be carried out by the Observational Study Monitoring Board (OSMB), and Steering Committee. Monitoring will include adherence to protocol, achievement of recruitment goals and patient.

An organizational chart for the BABY HUG Follow-up Study is presented in Exhibit 12-1.

12.2 PARTICIPATING UNITS

12.2.1 Steering Committee

The Steering Committee will comprise the Study Chairman, the Vice-Chairman, the Principal Investigator of the Data Coordinating Center, the NHLBI and NICHD Project Officers, all Clinical Center Principal Investigators , the Coordinator Chair, two Clinical Center Coordinators (by election) and, ex officio, the directors of the Core Laboratories, and the Data Coordinating Center Deputy Director.

12.2.2 Clinical Centers

The collaborating centers are funded by contracts from the NHLBI. A PI and a Coordinator should be identified at each Clinical Center. Exhibit 12-2 lists the Clinical Centers and the Principal Investigator.

A final recruitment report specifying the number of patients enrolled by each certified Clinical Center will be distributed after the end of enrollment.

12.2.3 Study Coordinator Committee

One BABY HUG Follow-up Study coordinator (Coordinator Chair) will be selected to have responsibility for organizing all the BABY HUG Follow-up Study coordinators into the Study Coordinators Committee - SCC. This person's responsibility will include:

1. foster enthusiasm for the BABY HUG Follow-up project;
2. act as a liaison between the Steering Committee and the SCC;
3. coordinate regular SCC conference calls; and
4. organize SCC meeting agenda and SCC project reports.

The SCC's responsibility will include:

1. development of coordinator writing projects;
2. attending Steering Committee meetings; and
3. participating in SCC conference calls to
    a. report enrollment progress,
    b. collaborate on enrollment successes/problems,
    c. team build, and
    d. develop writing plans.

12.2.4 Core Laboratories

The Core Laboratories have responsibility for receiving blood and urine samples from the Clinical Centers and performing specimen analyses.

12.2.5 National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) staff -- Blood Diseases Branch (Division of Blood Diseases and Resources) and Office of Biostatistics Research (Division of Prevention and Population Sciences) will participate with study investigators and key study personnel in all phases of the study. A member of the Blood Diseases Branch (Division of Blood Diseases and Resources) will serve as a voting member on the Steering Committee, and other study committees as appropriate.

The NHLBI will provide direction in the management of the contracts which fund the study, and assistance in developing solutions to major problems. An OSMB has been appointed by the NHLBI to provide overall monitoring of the study. The NHLBI OSMB reviews the data at six-month intervals. A progress report showing results according to the different treatment types (see Chapter 4 of the protocol) will be forwarded by the DCC to the OSMB at these times and their recommendations will be expeditiously implemented.

12.2.6 Data Coordinating Center

The Data Coordinating Center staff will include the Principal Investigator/Data Coordinating Center Director, Project Manager/Deputy Director, statistician(s), computer programmer(s) and coordinator(s). Data Coordinating Center staff for the BABY HUG Follow-up Study will provide expertise in the areas of study design, quality control, data processing and data analysis. Data Coordinating Center staff will provide biostatistical and epidemiological advice for the overall conduct of BABY HUG Follow-up and will collaborate with the BABY HUG Follow-up Study Investigators in all phases of the study including participant enrollment and Follow-up, preparing required statistical analyses, generating Core Laboratory work lists, report forms, blood specimen transmittal lists, and progress reports, and, assist in the preparation of manuscripts for publication. Data Coordinating Center staff will undertake the primary responsibility for the collection, processing, storage and analysis of the study data, as well as cooperating with the Operations Committee to ascertain that the provisions of the protocol are

carried out by each Clinical Center.

12.2.7 National Institute of Child Health and Human Development

A Memorandum of Understanding was signed between the NHLBI and NICHD during the BABY HUG Treatment study to allow the NICHD to perform pharmacokinetic (PK) studies under the Best Pharmaceuticals for Children Act (BPCA) to support a submission to the FDA for labeling of hydroxyurea for infants and very young children with sickle cell disease.

12.3 STUDY ADMINISTRATION

12.3.1 Study Chairman and Vice-Chairman

The Study Chairman and Vice-Chairman have been elected to represent the BABY HUG Treatment Study by the Steering Committee. The Study Chairman is Chairman of the Steering Committee. The Study Chairman is responsible for overall conduct of the study. The Vice-Chairman acts in place of the Study Chairman in case of the Study Chairman's unavailability.

12.3.2 Steering Committee

The Study Chairman will preside over the Steering Committee which will be responsible for overseeing the conduct of the study and writing of main papers as directed by the OSMB and as approved by the NHLBI.

12.3.3 Observational Study Monitoring Board

OSMB voting members will include experts in sickle cell anemia, the clinical use of hydroxyurea, biostatistics and bioethics, who are not connected with the study, and ex officio (non-voting) members -- the Study Chairman and the Data Coordinating Center Principal Investigator -- and representatives of the NHLBI and NICHD who will attend meetings to present information and receive recommendations. The OSMB will review Data and Safety Monitoring Reports, and make recommendations. The Operations Committee will report any unexpected or unusual findings to the OSMB which may be convened ad hoc for a special review of BABY HUG Follow-up any time circumstances so warrant. The OSMB will meet at least yearly, to review the annual BABY HUG Follow-up report. It will review safety issues as the trial

progresses and will evaluate treatment efficacy at pre-specified interim time points.

The BABY HUG Follow-up Clinical Center investigators are excused from the discussion. Data Coordinating Center staff take summary notes of the OSMB meeting from the end of the Executive Session through the presentation of study outcomes and discussion. At the end of the presentation of study outcomes and discussion, the Data Coordinating Center staff are excused for the OSMB to meet in a second Executive Session. The NHLBI representative is responsible for recording summary notes of the second Executive Session and the recommendations of the OSMB. At the end of the second Executive Session, the BABY HUG Follow-up investigators rejoin the OSMB for a preliminary review of OSMB recommendations. The NHLBI Executive Secretary of OSMB provides the summary notes and recommendations of the OSMB, in an expeditious and timely manner, to the Data Coordinating Center. The Data Coordinating Center communicates these recommendations to the BABY HUG Follow-up Steering Committee. At the next OSMB meeting, the OSMB votes to accept (or revise) the summary notes recording transactions of the meeting and recommendations.

12.3.4 Endpoints Evaluation Committees

Films and CDs received from the Clinical Centers will be reviewed on a regular basis by committees consisting of experienced clinicians who are familiar with the area of special study evaluations (e.g., liver-spleen scans, abdominal sonograms) and with the spectrum of illness in sickle cell anemia and who have no other connection with this study. They will receive materials for review from and return grading forms to the Data Coordinating Center for incorporation into the study database.

Exhibit 12-1

Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG Follow-up)

ORGANIZATIONALCHART

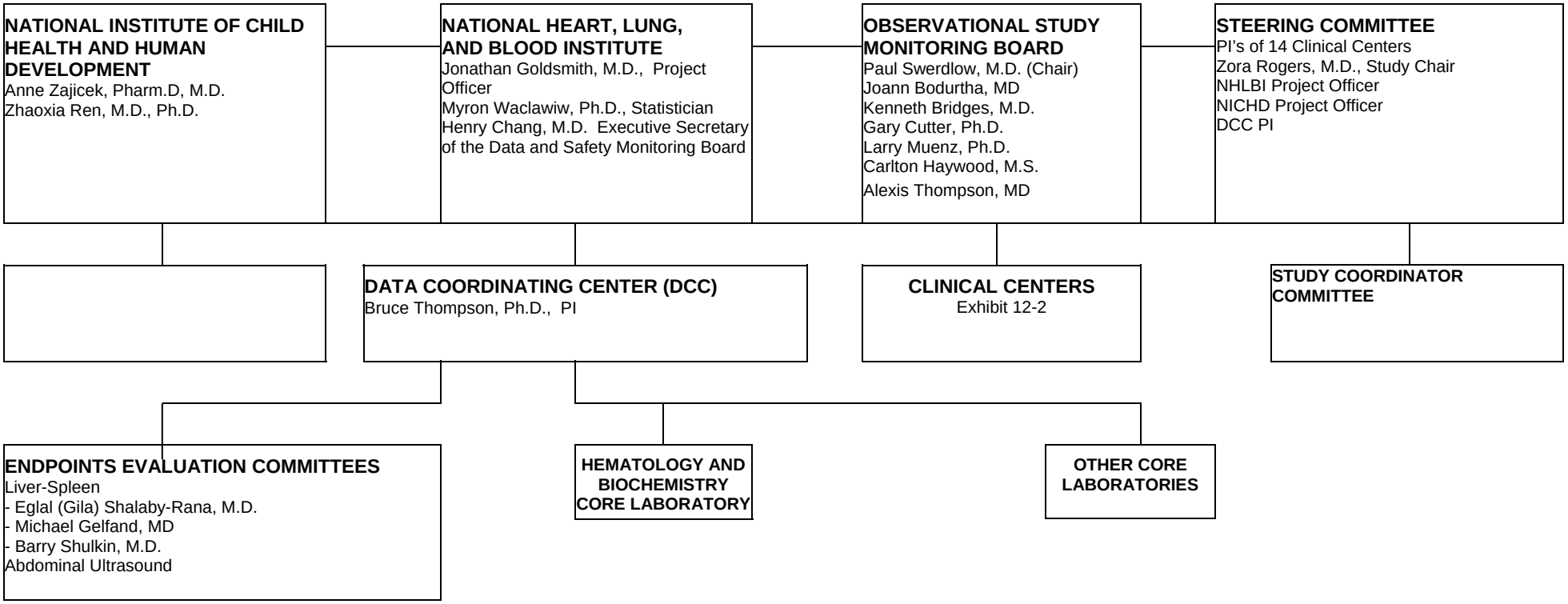

Exhibit 12-2
PARTICIPATING CLINICAL CENTERS

Children's National Medical Center, Lori Luchtman-Jones, M.D. - 01
(Washington, DC)

Duke University Medical Center, Courtney Thornburg, M.D. - 02
(Durham, NC)

Howard University College of Medicine, Sohail Rana, M.D. - 03
(Washington, DC)

Johns Hopkins University School of Medicine, James F. Casella, M.D. - 04
(Baltimore, MD)

Medical University of South Carolina, Sherron Jackson, M.D. - 05
(Charleston, SC)

St. Jude Children's Research Hospital, Winfred C. Wang, M.D. - 06
(Memphis, TN)

State University of New York - Brooklyn (SUNY), Scott T. Miller, M.D. - 07
(Brooklyn, NY)

University of Miami School of Medicine, Ofelia Alfarez, M.D. - 08
(Miami, FL)

University of Mississippi Medical Center, Rathi V. Iyer, M.D. - 09
(Jackson, Mississippi)

University of Texas Southwestern Medical Center, Zora R. Rogers, M.D. - 10
(Dallas, TX)

University of Alabama, Birmingham, Thomas Howard, M.D. - 11
(Birmingham, AL)

Drexel University, Norma Lerner, M.D. - 12
(Philadelphia, PA)

Emory University School of Medicine/CHOA, R. Clark Brown, M.D., Ph.D. - 13
(Atlanta, GA)

Wayne State University, Ingrid Sarnaik, M.D. - 14
(Detroit, MI)

<u>DATA COORDINATING CENTER</u>
Clinical Trials & Surveys, Corp. (Baltimore, MD)
Bruce W. Thompson, Ph.D., Principal Investigator

<u>PROJECT OFFICE</u>
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute (Bethesda, MD)
Jonathan Goldsmith, M.D., Project Officer
Henry Chang, M.D., Executive Secretary of the Observational Study Monitoring Board

Division of Prevention and Population Sciences, Office of Biostatistics Research
Myron Waclawiw, Ph.D., Statistician

PEDIATRIC HYDROXYUREA PHASE III CLINICAL TRIAL
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CHAPTER 13

POLICY MATTERS

13.1 INTRODUCTION

Procedural guidelines are established to ensure that all Investigators adhere to the protocol, to facilitate optimum use of data generated by the study, and to ensure optimal use of the resources of the Central Units and Data Coordinating Center.

13.2 PROTOCOL DEVIATIONS

The Data Coordinating Center will create a list of protocol deviations. Protocol deviations are those which impede the progress of the study, such as not filing reports in a timely fashion (form delinquencies) and excessive delays in supplying materials (e.g, scans, other images or event reports) for central review.

The Data Coordinating Center will document protocol deviations in performance reports, as well as notifying the Clinical Centers of them. Repeated protocol deviations which are not corrected will result in reports to the Data and Safety Monitoring Board (OSMB), the NICHD and the National Heart, Lung, and Blood Institute (NHLBI).

13.3 CHANGES IN PRINCIPAL INVESTIGATORS

It is expected that changes in Principal Investigators (PIs) will occur in some of the Clinical Centers. These changes may be necessitated by movement of the Principal Investigators to another institution, illness, retirement, or change in responsibility within the same institution. In this situation, retention of the established/experienced nurse coordinator or data manager may help ensure that the Clinical Center can continue to function effectively. When such a change occurs, it is understood that the contractual arrangement between the NHLBI and the Clinical Center will be reviewed and that a new PI will need to be approved by

the NHLBI. The members of the Steering Committee are available to discuss and provide input into the decisions that are made in the interim.

The Clinical Centers and/or their representatives, the Data Coordinating Center, and the NHLBI and NICHD Project Offices should all participate in any decisions which involve turnover of Principal Investigators and/or Clinical Centers.

13.4 TYPES OF BABY HUG FOLLOW-UP STUDY RESEARCH

BABY HUG Follow-up Study research and the resulting presentation and publications may be grouped into the following study categories.

1. Endpoint studies;
2. Data bank studies;
3. Ancillary studies.

The Steering Committee will exercise responsibility for all data bank, and ancillary studies, and for all publications and presentations evolving from BABY HUG Follow-up Study research, through the Publications Committee. BABY HUG Follow-up Investigators have agreed that all BABY HUG Follow-up research is collaborative in nature. No investigator will publish BABY HUG Follow-up Study data from any one Clinical Center or group of Clinical Centers without the written approval of the Publications Committee, the NICHD and the NHLBI.

Investigators at all BABY HUG Follow-up Clinical Centers, including the Data Coordinating Center and the NHLBI and NICHD Program Offices, have equal status with regard to developing protocols, participating in such studies as are approved and collaborating in the development and publication of research papers based on BABY HUG Follow-up material.

The procedures in this section for endpoint, data bank, and ancillary studies, and for publication of BABY HUG Follow-up research results are similar to those used in other cooperative clinical trials. These procedures are intended to protect the interests of all Investigators and patients in the trial, namely, to assure that study data conform to the requirements of study design, are accurately presented, authorship is appropriately

acknowledged, and the text of all publications is well written with proper attention to the protection of patient privacy. All BABY HUG Follow-up publications are subject to review and approval by the NHLBI and NICHD.

13.4.1 Data Bank Studies

A data bank study is a study which uses data routinely collected on patients when they are enrolled in a clinical trial and analyzes these data to answer some scientific question.

13.4.2 Ancillary Studies

An ancillary study is a study which uses supplementary data collected on patients who are enrolled in a clinical trial, over and above the data collection required by the current Protocol. Such studies are usually restricted to consideration of a specific test technique or involve only supplemental data collected on some or all study patients.

Approval and participation in ancillary studies are considered by the Steering Committee, the NICHD and National Heart, Lung, and Blood Institute (NHLBI) with the advice of independent review committees (the OSMB or the Protocol Review Committee). Proposals for ancillary studies are submitted to the Data Coordinating Center which distributes them to the Steering Committee for scientific review and Clinical Center Principal Investigator consideration with regard to feasibility and interest in participation in the ancillary study in each Clinical Center. Steering Committee members reply to a ballot distributed by the Data Coordinating Center indicating their approval or disapproval of the ancillary study, the priority they would accord the ancillary study and whether or not their Clinical Center would participate in the ancillary study. Approval requires a majority vote.

13.5 CLINICAL CENTER ACCESS TO BABY HUG FOLLOW-UP DATA FILES AT THE END OF THE STUDY

At the end of the study, Data Coordinating Center staff will produce a well documented data tape containing a refined (and reduced) set of the BABY HUG Follow-up Study data for the purpose of analysis by the BABY HUG Follow-up Study Investigators and eventual release to

the public domain in accordance with NHLBI policy. Clinical Center Investigators may analyze the data on this data tape in their own centers, but prior to submission of articles for publication must submit the analyses proposed for publication to the Data Coordinating Center, where they will be reviewed and computations replicated. Clinical Center Investigators who perform their own analyses are responsible for obtaining all support necessary for the data bank or ancillary study outside of regular study resources. The Data Coordinating Center will be the center of study analysis activities as long as the BABY HUG Follow-up Investigators continue in their collaborative efforts.

13.6 PUBLICATIONS

13.6.1 Papers Regarding Overall Study Issues

1. "Overall study issues" are defined as those related directly to assessment/analysis of the study's primary objectives. The Steering Committee will make writing assignments for initial drafts of such papers based on interest from members of the Steering Committee.
2. The authorship of these papers will include the Investigators, the Data Coordinating Center Director, and others as deemed appropriate by the Steering Committee; order will be determined by the Publications Committee. Other key personnel with institutional affiliations will be listed as a footnote. These will include the Center Coordinators and others who have a role in the study. NHLBI and NICHD staff will not be co-authors of the primary results manuscript. NHLBI and NICHD staff will participate as co-authors of the design and secondary analyses papers as appropriate to intellectual interest.
3. These manuscripts are to be sent to all members of the BABY HUG Follow-up Study Steering Committee for comment prior to its submission. Members must respond with comments or an indication that the manuscript is acceptable, and state their willingness to accept authorship, within 10 days of distribution of a manuscript draft.

13.6.2 Other Publications

13.6.2.1 Papers/Manuscripts

1. Publications that fall under this policy are those that involve BABY HUG Follow-up patients and/or include any data, from one or more Centers that participate in BABY HUG Follow-up or any of its ancillary studies. Local Center studies that involve BABY HUG Follow-up patients but no study data collected expressly for BABY HUG Follow-up do not fall under this policy.
2. All study Investigators and key personnel, described above, will be encouraged to submit proposals for papers to the Publications Committee. Proposals will be submitted in a defined format, which will state the research question or hypothesis and include a brief background statement supporting its importance (see Exhibit 13-1 Publications Worksheet). All topics must be reviewed by the Data Coordinating Center (to determine if the study data will support the question) and be approved by the Operations Committee. If more than one investigator submits the same or overlapping proposals, primacy will be determined by the one dated earliest. A listing of projects will be prepared and maintained by the Publications Committee.
3. When approved, one individual will be assigned to serve as Chair of a Writing Committee. Usually, the person proposing the topic will assume this role. However, before an investigator is awarded the chairmanship of a second topic, investigators will be polled to allow other interested investigators an opportunity to serve as lead author/Writing Committee chair.
4. Each Writing Committee will include a representative from the Data Coordinating Center and approximately 5-6 other authors. Approved writing projects will be announced so that Investigators may request membership on the committee. If more Investigators wish to participate than can be accommodated, Investigators

enrolled on fewer writing committees will be given priority. Investigators wishing to serve on multiple committees may be asked to prioritize their choices; an attempt will be made to assign topics to those who indicate a high level of interest.

5. For ancillary projects approved by the Steering Committee, the ancillary project PI will be the Writing Committee Chair for any manuscripts that arise from his/her research. The Writing Committee membership will be selected by that individual and will consist of some or all of the BABY HUG Follow-up PIs who are participating on the project. BABY HUG Follow-up will be acknowledged in any publication that uses data obtained as part of the ancillary project. Review of manuscripts by the Publications Committee and NHLBI-NICHD will follow the same process as described above.
6. The Publications Committee will determine the priority with which topics will be analyzed by the Coordinating Center.
7. Next, analysis will begin; the manuscript must progress in a timely manner. In general, a draft manuscript should be completed within six months of availability of the required data analyses; Committee Chairs are encouraged to format their papers and write Introduction, Methods and a preliminary Discussion even prior to Results being available. If progress is unsatisfactory, the Publications Committee will propose a replacement for the Writing Committee Chair. A replacement must be approved by the Steering Committee.
8. All authors are expected to be full participants in manuscript preparation. If the Writing Committee Chair determines that a member is not participating, s/he may request that person's removal by notifying the Publications Committee.
9. The Publications Committee will maintain a list of Writing Committee Chairs and membership. This will be presented at each meeting of the Steering Committee along with the priority and status of any manuscripts. It is the responsibility of the

Publications Committee to recognize potentially overlapping writing projects and consolidate proposals where necessary. If needed, disputes regarding any redistribution of projects or responsibilities can be referred to the Steering Committee for resolution.

10. All publications will include the names of all members of the Writing Committee as masthead authors followed by the phrase, "for the Investigators of the Pediatric Clinical Trial of Hydroxyurea in Sickle Cell Anemia (BABY HUG Follow-up Study)". The Writing Committee Chair will determine the order of authorship based on effort and contribution. Usually the name of the Writing Committee Chair will be listed first. The Chair may choose to add the names of other individuals to the author list depending on participation in the design/performance of the project and/or preparation of the manuscript. All publications will acknowledge the support of NHLBI and NICHD.
11. The name, title and affiliation of all key personnel will be listed in a footnote to all manuscripts submitted. This listing will be established and maintained by the DCC.
12. The lead author will usually be designated as corresponding author. Requests for reprints will be directed to that person. The DCC will ensure that all participating centers receive copies of all study publications.
13. All manuscripts will be submitted to the Publications Committee prior to submission for publication. The Publications Committee will choose two to three Investigators as reviewers. The PI of the DCC will review the statistical analysis of each manuscript for accuracy even if local statistical resources are used for that data analysis. The review process will be accomplished in a period of no more than two weeks.
14. After suggested changes have been considered, the manuscript will be submitted to the Contracting Officer and NHLBI Project Officer at least 45 days prior to

submission to a journal. In order to balance the oversight responsibility of the National Heart, Lung, and Blood Institute (NHLBI) with the authorization provided the contractor by the Rights in Data clause of this contract, the NHLBI has established a process to review manuscripts produced under this contract. Please note that the NHLBI does not require contractors to seek the Institute's approval of manuscripts.

15. In order to have sufficient time to conduct a meaningful review, the Institute's Project Officer and Contracting Officer must have advance notice of intent to submit a manuscript for publication at least 45 days prior to submission to the publisher. The advance notice should briefly describe the plans for publication of the manuscript.
16. Concurrently or as soon as possible following this notice, the manuscript should be provided to the Executive Secretary for OSMB review and the Project Officer for final approval by NHLBI/NICHD. Any comments from the NHLBI/NICHD will be provided in writing within 15 days after receipt of the manuscript by the Project Officer. Comments expressed by the NHLBI about the manuscript shall not be a cause for action under the Disputes clause of the contract by either NHLBI or the contractor, since the NHLBI does not approve manuscripts and draft manuscripts are not contract deliverables.

13.6.2.2 Abstracts

1. Abstracts that fall under this policy are those that involve BABY HUG Follow-up patients and/or include any data, whether from one or many Centers, that were acquired as part of BABY HUG Follow-up or any of its ancillary studies. Local Center studies that involve BABY HUG Follow-up patients but no study data do not fall under this policy.

2. Abstracts may be prepared for submission to any appropriate meeting. Usually the topic will be based on or related to one already assigned to an established Writing Committee. Alternatively, topics that differ from those established for Writing Committees may be proposed utilizing the Publications Worksheet (See Exhibit 13-1).
3. Abstract topics must be approved by the Publications Committee before data will be made available and analysis begun by the Data Coordinating Center. In addition, the Publications Committee Chair, the PI of the Study and the DCC will confer and attempt to balance the desire to get abstracts presented with the need for ongoing statistical analyses for the main study or manuscript preparation. Accordingly, approval in concept may not mean that the DCC can respond to all abstract requests in the time frame desired by the proposer. Thus, Investigators are strongly encouraged to plan abstract proposals well in advance of deadlines so that there is sufficient time to prepare abstracts.
4. The decision to submit abstracts that arise from Ancillary Projects will be the responsibility of the individual managing the project. Some projects may not require DCC assistance and therefore do not need to go through the above prioritization and approval process. The Writing Committee should be chosen from those Principal Investigators who are project participants.
5. Authorship of abstracts will be determined as for manuscripts (described above), depending on whether the abstract pertains to overall study issues or a subissue arising from a writing project or ancillary project.
6. An abstract must be submitted to the Publications Committee Chair at least 14 days prior to the deadline for submission. Abstracts must therefore be sent for comment and approval by potential authors 18-21 days prior to the submission deadline; potential authors who do not respond promptly may be removed. Upon

receipt, the Publications Committee Chair will circulate the abstract to the Steering Committee for immediate review, and any comments will be returned to the Writing Committee Chair and Publications Committee Chair within four days (which is 10 days prior to submission deadline). A **final** version will be forwarded for final approval by the Publications Committee Chair to the NHLBI/NICHD Project Officer and OSMB Executive Secretary at least seven days prior to submission deadline for immediate review and approval.

13.7 CONFLICT-OF-INTEREST

BABY HUG Follow-up Investigators and their immediate family will not buy, sell, or hold stock options in any of the companies* providing medication (or making competing products) under study from the time the recruitment of patients for the trial begins until funding for the study in the Investigator's unit ends and the results are made public; or from the time the recruitment of patients for the trial begins until the Investigator's active and personal involvement in the study or the involvement of the institution conducting the study (or both) ends.

Each Investigator will agree not to serve as a paid consultant to the companies during these same periods. The guidelines will also apply to the Investigator's spouse and dependents.

Certain other activities are not viewed as constituting prohibited conflicts-of-interest but must be reported annually to the Data Coordinating Center: the participation of Investigators in education activities supported by the companies (permitted only if no honorarium is paid to the Investigator); the participation of Investigators in other research projects supported by the companies; and, occasional scientific consulting to the companies on issues not related to the products in the trial and for which there is no financial payment or other compensation. The

*Bristol-Myers Squibb

BABY HUG Follow-up conflict-of-interest policy will incorporate the NHLBI and U.S. Food and Drug Administration (FDA) policies on conflict-of-interest for Investigators.

The BABY HUG Follow-up Investigators will not accept any restraint on freedom of publication.

EXHIBIT 13-1

BABY HUG Follow-up Publications Worksheet

Submit this worksheet to the Publications Committee Chair. If you would like to provide more detail about your proposal, you may attach one or two additional pages. Please note that the Committee must approve the final draft of your paper before it is submitted.

Date submitted to the Publications Committee _____

Proposed title of paper

_____

Possible journal for submission?

_____

Members of Writing Committee

Proposed Chair _____

Possible Members _____

_____

_____

Introduction (a brief statement of the scientific context and interest in this question):

Main questions or issues to be addressed by this paper:

Methods pertinent to this paper (e.g., inclusion/exclusion, data required, statistical analysis):

Anticipated Results:

Figures/Tables Required:

Discussion: Provide a few points that you plan to discuss regarding the limitations, implications, and significance of the findings.

Conclusions:

Key References:

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CHAPTER 14

USE OF THE BABY HUG FOLLOW-UP STUDY WEBSITE

14.1 OVERVIEW

The BABY HUG Follow-up Study Web Site is available for use by all BABY HUG Follow-up Study Clinical Center and Project Office staff. For questions about the web site, see the BABY HUG Follow-up Study Address Directory page for the Programmer/Analyst at the DCC.

To access the BABY HUG Follow-up Study web site, type http://www.studyctms.com into your browser address window. Authorized users will be confidentially given a user log-on account and password. (See Exhibit 14-1.) Your connection to the BABY HUG Follow-up Study web site will be terminated after 20 minutes of inactivity. If that occurs, you will need to log back into the web site to continue.

Most documents available on the BABY HUG Follow-up Study web site are in Portable Document Format (PDF). Documents in PDF preserve the exact look and content of the originals. Adobe Acrobat Reader 4.0 or higher is required to read and print the PDF documents. This program is free and is available from Adobe at:

http://www.adobe.com/products/acrobat/readstep.html.

Each of the BABY HUG Follow-up Study web site pages has a link to Adobe. When installing the program from the Adobe web site, follow the directions given on that web site. To open a PDF document with the Adobe Acrobat Reader on the BABY HUG Follow-up Study website, click on the file name.

14.2 CONTENTS OF THE BABY HUG FOLLOW-UP STUDY WEBSITE

The BABY HUG Follow-up Study home page (see Exhibit 14-2) identifies and provides links to the categories of information available on the web (i.e. Dashboard Objects, Visit Management). To review the contents of each category, click on the category heading. The page for that category is then displayed. Each page lists the documents available in that category.

The BABY HUG Follow-up Study Documents page identifies and provides folders for each Clinical Center and for essential documents.

Listed below are the names of all the folders you will find on the Documents page. The first seventeen folders listed can be seen on Exhibit 14-4. More folders may be added as needed throughout the course of the study.

- Protocol
- Manual of Operations
- Study Tools
- Data Coordinating Center Documents
- Internal Testing Site Documents
- Study Forms
- Memos
- Minutes
- Publications
- Reports
- FAQ's

Form Entry

Users new to the BABY HUG Follow-up Study must apply for "Data Entry and Content" on the BABY HUG Follow-up Study User Application (see Exhibit 14-3) to have access to Form Entry on the BABY HUG Follow-up Study web site. This category will be listed on the BABY HUG Follow-up Study home page only for users who have applied for and are authorized for this type of access.

For Clinical Center staff who were previously certified for the BABY HUG Treatment Study, an application is not necessary. Upon certification, these users will be sent a password via e-mail from "Webmaster" and will use their individual work e-mail addresses for their username.

14.3 SYSTEM REQUIREMENTS TO ACCESS THE BABY HUG FOLLOW-UP STUDY WEBSITE

In order to use the web site, the user at the Clinical Center must have a computer that has the following configuration.

1. Connection to the Internet at 56 KB or higher.
2. A PC running Windows 2000, XP or VISTA or an Apple running MAC OS X.
3. Microsoft Internet Explorer 6.5 or greater of Firefox 2 (PC or MAC) or later. The browser must be set to accept cookies.

14.4 USER APPLICATION

Each staff member at the Clinical Center designated to use the web site must complete a BABY HUG Follow-up Study User Application (See Exhibit 14-3) and send it to the BABY HUG Follow-up Study DCC by facsimile transmission (443-524-2320).

Clinical Center staff may request authorization for 'Data Entry and Content'; this allows the user to browse and print the web site content as well as to enter, modify and view data for patients enrolled in his/her Clinical Center. Before requesting 'Data Entry and Content' use, the system requirements for Internet data entry should be reviewed. (See Chapter 7.)

14.5 PRINTING STUDY FORMS OR OTHER DOCUMENTS ON THE BABY HUG FOLLOW-UP STUDY WEBSITE

From the 'Forms' section, click on the file name to open a PDF document. (Any pop-up blockers may need to be disabled.) The Adobe Acrobat Reader automatically opens and the document is displayed on the screen. The document can then be read on the screen or printed using the Adobe Acrobat menu.

EXHIBIT 14-1
BABY HUG FOLLOW-UP STUDY

StudyCTMS Login Page (www.studyctms.com)

EXHIBIT 14-2

BABY HUG Follow-up Study Home Page

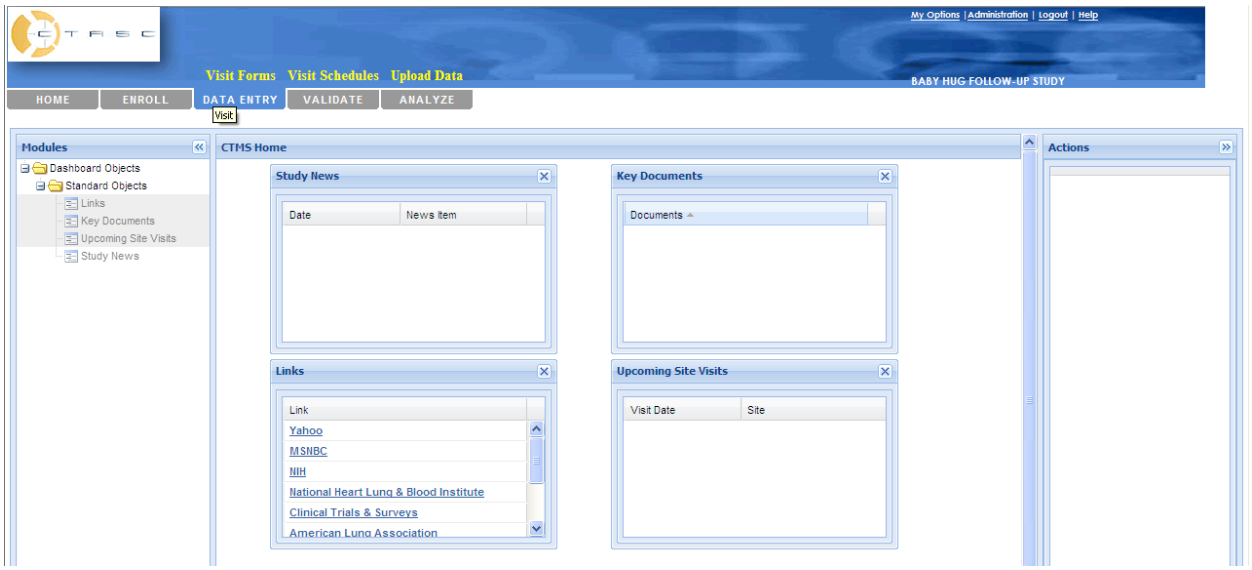

EXHIBIT 14-3
BABY HUG Follow-up Study User Application

BABYHUG Follow-Up Study
User Application

Complete one form per user.
Please print or type clearly.
Fax to C-TASC at (443) 524-2320

Date: _____

Site Number/Name: _____

User Name: _____

User e-mail: _____

User Phone Number: area code ( ) _____

Computer / Operating System: _____

Browser / Version: _____

Certification Requested: (Select One)

☐ Content Only – The user may browse web site content such as manuals and forms, but may not enter, modify or view data.

☐ Data Entry and Content – The user may browse web site content such as manuals and forms, and may enter, modify and view data.

For Computer Services Use Only!

		Comments:
Test IDs:	_____	
Passed Comparison:	_____	_____
Date Certified:	_____	_____
Completed by:	_____	_____
USER LOGON Assigned:	_____	_____
USER PASSWORD Assigned:	_____	_____
USER NUMBER Assigned:	_____	_____

wmr:/E:/BABYHUG Follow-up/Forms/User-Appli.doc

EXHIBIT 14-4
BABY HUG Follow-up Study Documents Page