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

# 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

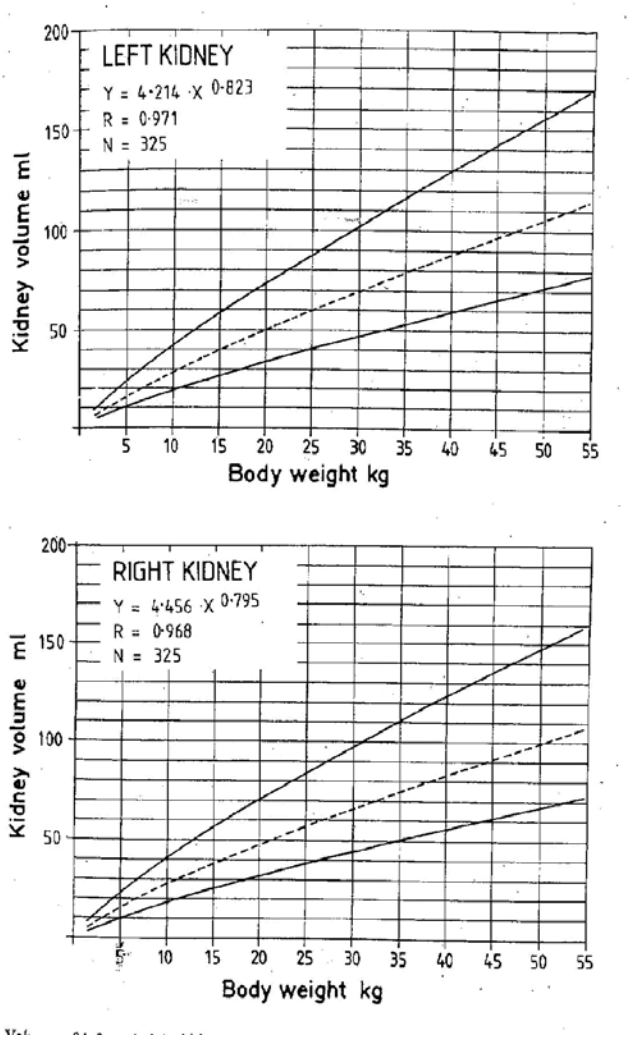
Representative images of both kidneys will be obtained in the longitudinal and transverse planes and the cortical echogenicity will be determined to be either normal or abnormal.

#### 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

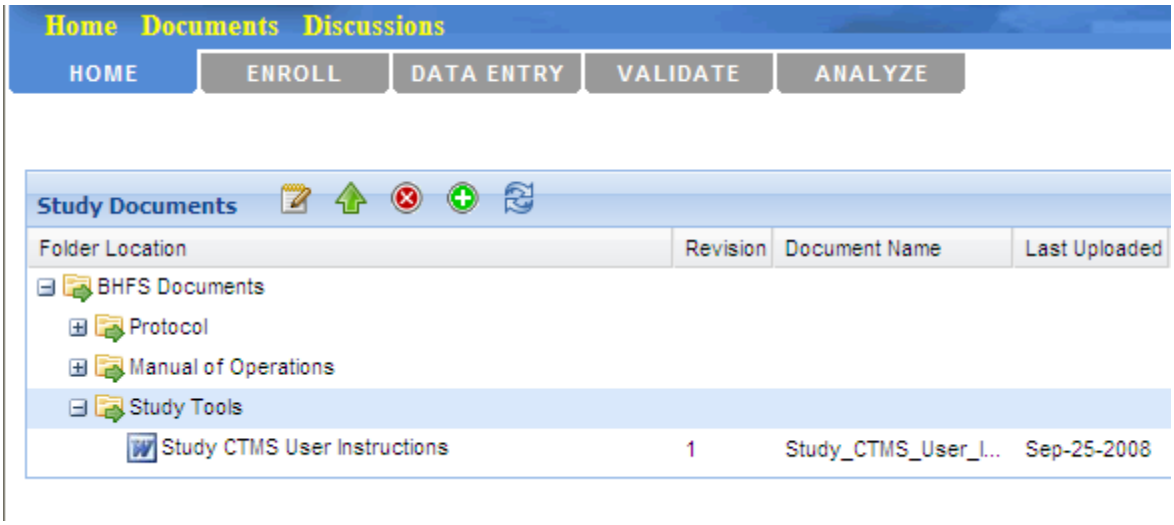
All source documents must be signed and dated. All modifications to the source document must be properly recorded (single-line strikeout so that the original text is still readable, initialed and dated, or similar process electronically, dependent upon your Center's electronic system formatting). The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



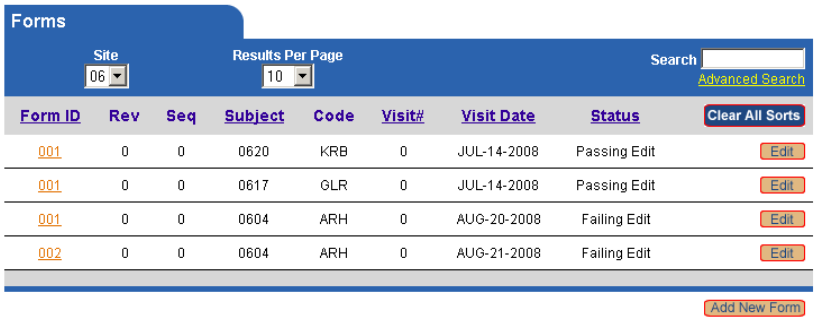

#### 7.1.2.1 Internet Data Entry System User Access

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.

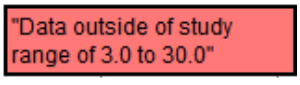
#### 7.1.2.5 Save Your Work

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.

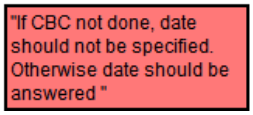
The Error column shows a count of all form errors that have NOT been validated or corrected to date. To enter a form to edit, the user clicks on the **Edit** button to the right of the form they desire to edit.

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

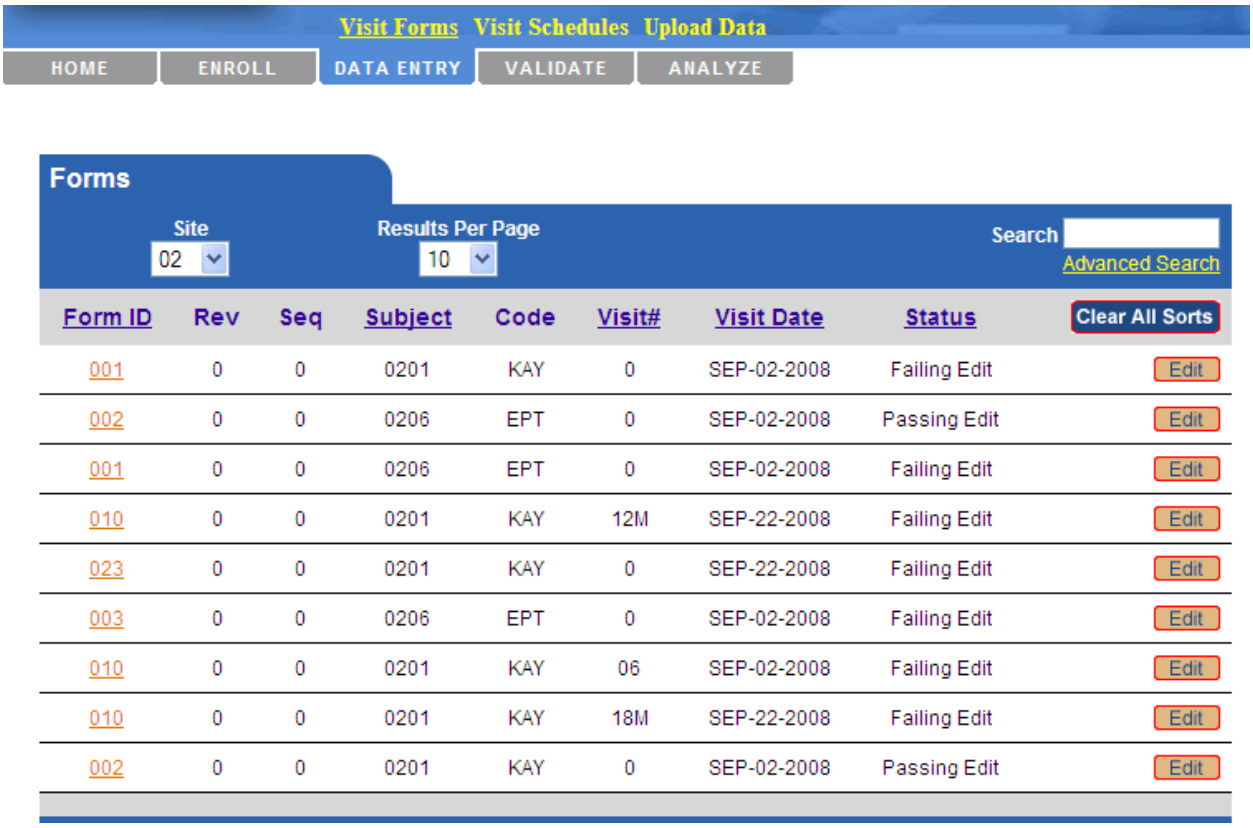
In the event that forms cannot be transmitted due to equipment failure (e.g., the server is down at the DCC or at the Clinical Center) the forms should be keyed as soon as the system becomes available. However, in the event of an SAE, the forms should be faxed to the DCC using the dedicated BABY HUG 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:




| Form ID | Rev | Seq | Subject | Code | Visit# | Visit Date | Status | |
|---|---|---|---|---|---|---|---|---|
| 001 | 0 | 0 | 0201 | KAY | 0 | SEP-02-2008 | Failing Edit | Edit |
| 002 | 0 | 0 | 0206 | EPT | 0 | SEP-02-2008 | Passing Edit | Edit |
| 001 | 0 | 0 | 0206 | EPT | 0 | SEP-02-2008 | Failing Edit | Edit |
| 010 | 0 | 0 | 0201 | KAY | 12M | SEP-22-2008 | Failing Edit | Edit |
| 023 | 0 | 0 | 0201 | KAY | 0 | SEP-22-2008 | Failing Edit | Edit |
| 003 | 0 | 0 | 0206 | EPT | 0 | SEP-02-2008 | Failing Edit | Edit |
| 010 | 0 | 0 | 0201 | KAY | 06 | SEP-02-2008 | Failing Edit | Edit |
| 010 | 0 | 0 | 0201 | KAY | 18M | SEP-22-2008 | Failing Edit | Edit |
| 002 | 0 | 0 | 0201 | KAY | 0 | SEP-02-2008 | Passing Edit | Edit |

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** |
| __ __ __-__ __-__ __ __ __ | __ __ __-__ __-__ __ __ __ | | | | | |
| __ __ __-__ __-__ __ __ __ | __ __ __-__ __-__ __ __ __ | | | | | |
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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

### 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 |

## REGULATORY AFFAIRS

| | | 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 |

## SOFTWARE DEVELOPMENT

| | | 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 |

## STUDY MANAGEMENT

| | | 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**
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# 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.

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# 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

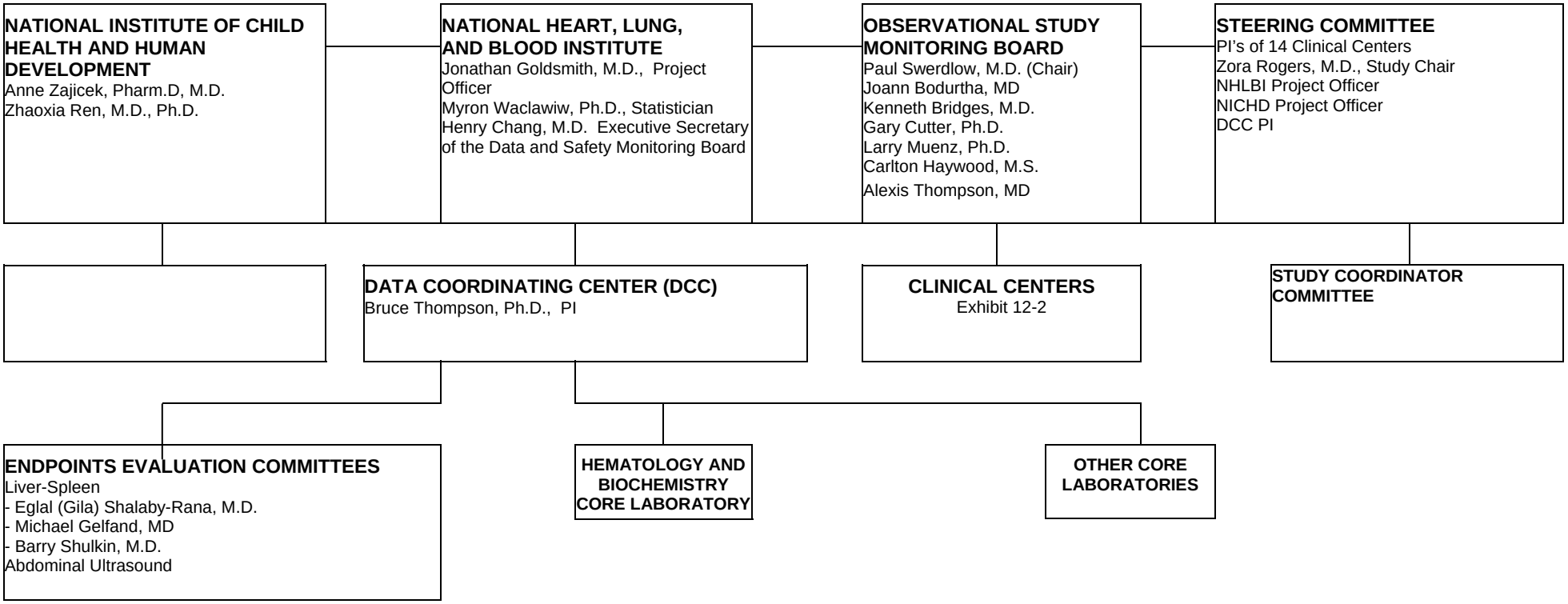

**Exhibit 12-2**
**PARTICIPATING CLINICAL CENTERS**

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

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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:

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

# 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

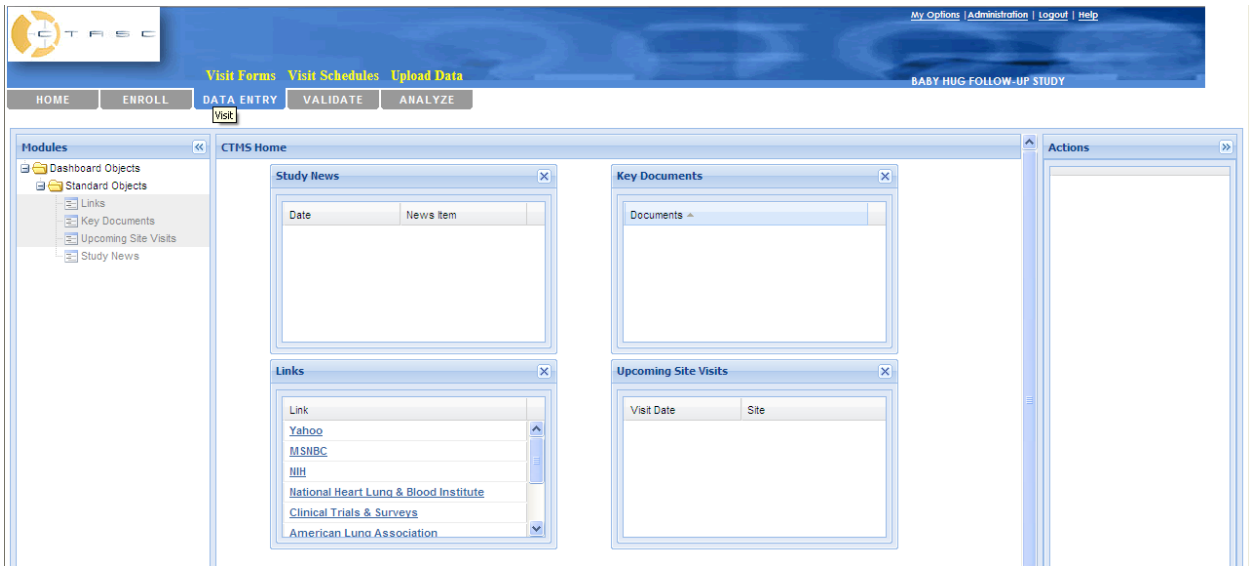
From the ‘Forms’ section, click on the file name to open a PDF document. (Any pop-up blockers may need to be disabled.) The Adobe Acrobat Reader automatically opens and the document is displayed on the screen. The document can then be read on the screen or printed using the Adobe Acrobat menu.

# 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