INFORMED CONSENT TEMPLATE

PURPOSE, PROCEDURES AND LENGTH OF STUDY

We are asking you to agree to your child's participation in a BABY HUG follow-up study in which children will continue to make regular clinic visits with the study doctors until December 2011. The BABY HUG treatment study was designed to see if treatment with the drug hydroxyurea (also referred to as HU) in children with sickle cell anemia could prevent organ damage, especially in the spleen and kidneys. There was also a chance that treatment could prevent "painful crises", lung disease, heart failure, stroke and blood infection by reducing the number of sickle-shaped cells in you child's bloodstream. If treatment with hydroxyurea provides a benefit, it will be important to determine how long that benefit continues. Another important part of this study is to investigate the long-term safety of HU. Follow-up of your child will provide important information concerning these issues.

Families may choose to participate in one of two ways. The first is known as "active follow-up". Choosing this type of follow-up means that your child will come for clinic visits at least every 4 months until age 5 and then at least every 6 months. The same laboratory testing, imaging procedures and behavioral testing that were done during the BABY HUG treatment study will be done in the follow-up study, except that the frequency of testing will be less. You may accept or decline any test and still remain in the "active follow-up" group.

The other follow-up group is known as the "passive follow-up" group. In this group the schedule of clinic visits and the testing done will again be at least every 4 months until age 5 and then at least every six months. However, we will only collect information from routine tests which usually include a complete blood count and measurement of your child's height, weight and head circumference at each visit. We will also collect information about illnesses that your child has during that time and how they were treated.

If you choose to participate in either group, we will go to your child's medical record to collect clinical information about your child since he/she exited the BABY HUG treatment study, if this is necessary.

Regardless of which follow-up type you choose, you will be able to decide with your doctor's advice, whether you want your child to be treated with hydroxyurea during this follow-up period. The decision to treat your child is a clinical decision made only by your family and your doctor. Once the decision is made, you, your doctor, and the doctors working in the study will know that your child is taking hydroxyurea. You can decide to stop HU treatment of your child at any time. We will not tell you which treatment your child received during the BABY HUG treatment study at this time. We plan to tell you the results of the BABY HUG treatment study after the last child completes it, about July 2009. We will also tell you at that time, whether your child received hydroxyurea or placebo. At the end of the follow-up study your family will be informed of the results and any new recommendations from the study doctors.

STUDY TESTS TO BE PERFORMED

Passive Follow-Up Group

At each clinic visit every four to six months, we will ask you questions concerning your child's health since the last visit. We will record the results of physical examinations and laboratory tests performed as part of routine clinical care. If your child has any major health problems between clinic visits including the usual complications of sickle cell disease and especially those that require hospitalization, please tell the BABY HUG study staff immediately.

If your family plans to move from the area, the study coordinator will contact you at the appropriate intervals to obtain information on clinical events. We will request any information relevant to the study regarding your child's health from other health care providers. You will have to sign a release for us to obtain that information.

Active Follow-up Group

If you agree to have your child in the active follow-up group, you agree to allow the reporting of the same clinical information as in passive follow-up, as well as additional tests to check the function of your child's spleen and kidneys, and neuropsychological development. These tests will be performed only once, approximately four years after your child was enrolled in the BABY HUG treatment study. Each of these tests may require a separate visit. In addition, a test will be done to measure the blood supply to the brain. This test will be performed twice, at approximately 3 and 4 years after you child was enrolled in the BABY HUG treatment study.

Tests requiring radiation to evaluate the function of the spleen and kidneys will be performed in exactly the same way they were done in the BABY HUG treatment trial. For each test, small doses of radioactive material will be given in your child's vein. We will use a camera sensitive to radioactivity to take pictures of your child's spleen. The radioactive material will leave your child's body in urine or stool by the next day. At the time of the kidney test, we will take three blood samples over four hours. In addition, the function of the kidneys will be checked by collecting a sample of urine for analysis.

In order to monitor your child's brain growth and development, neuropsychological testing will be performed. In the event your child develops symptoms suggestive of brain dysfunction, a Magnetic Resonance Imaging (MRI) test will be done. This test uses magnetic waves to form a picture of the brain. There is no exposure to radiation with this study. This test would be done even if your child was not part of the study at the time the symptoms occurred.

RISKS: For those in the active follow-up group.

The needle used to take blood or give radioactive material will cause a sharp pain at the time it goes into the skin. Sometimes a bruise will form at the place the needle goes into the skin. There is also a small chance of infection from the IV line or venous stick.

If your child takes part in this research, he or she may have one or more medical imaging studies. The tests your child may have include a liver-spleen scan and a DTPA scan. These tests involve a small amount of radiation which has been compared to the amounts that people encounter naturally in daily life from space and from rocks in the soil. This natural radiation is greater at higher altitudes. Your child would receive about the same amount of radiation as he or she would get from living in a high altitude city such as Denver for 1 ¼ years. The radiation dose we have discussed is what your child will receive from this study only and does not include any exposure he or she may have received or will receive from other tests.

BENEFITS

No one knows whether or not the study treatments given in BABY HUG treatment study will help your child. The results of this follow-up study, along with those from the BABY HUG treatment study, will help doctors decide in the future if and when to give this medication to young children with sickle-cell anemia and how long to give it.

FREE CHOICE

Your child's participation in the long-term follow-up study is up to you and is your free choice. You are free to take your child out of this study at any time. If you take your child out of the study or do not take part in the study, we will still be willing to take care of your child as always. The choice other than to continue follow-up in the study is to go on with standard care for sickle cell anemia with your child's doctor. You and your child's doctor may plan to use or not use hydroxyurea. Some children with sickle cell anemia get other treatments that may be possible for your child. These treatments include blood transfusions and bone marrow transplants. Your choice to continue on in the study will not change the way your child is treated in our clinic. In or outside of the study, we want to give the best care for your child.

COSTS

All costs that are considered part of routine clinical care will not be paid by the study. Routine

care will be billed, as before, to you and or your health insurance provider. Costs related to laboratory tests or procedures performed in the active follow-up group will be paid for by the study**.** If you decide to have your child take Hydroxyurea, the costs of the medication and the laboratory studies to monitor its effects will be billed to you and your health insurance provider.

PAYMENT

Each family with a child in active follow-up at this clinic will receive $ 50.00 for each visit required to perform the additional tests needed, to cover the cost of travel, meals, other expenses to the family and use of time and resources for being in the study.

PRIVACY

You have a right to privacy. All facts in this study that can single out your child or family will remain private. A number system is used for patient files that does not allow patients to be known to anyone outside this center. Your child will not be named in reports of results from this study. Your child's medical reports and family data will be kept private. At the end of the study a computer file of the study results will be made for future use. This data file will not have your child's name, your name or any facts that could be linked to your child or family directly. The computer file may be used by other doctors to study sickle cell anemia.

You ☐ agree ☐ do not agree _____ for the data file to include your child's information.
Initials

Data may be given to the National Institutes of Health, the Food and Drug Administration or other U.S. or state agency as required.

LIMITS

The <<insert Clinical Center name>> is not set up to provide compensation for subjects who may incur injuries as a result of being in this research. This means that while all study doctors will do everything possible to provide careful medical care and safeguards in the

conduct of this research, the medical center will not offer to pay for injury resulting solely from the research itself.

You can discuss the rights of research subjects with the Chairman of the Medical Center's Institutional Review Board, telephone number ( ). This board is composed of doctors and lay people who have reviewed and approved this study. Dr. _____, Principal Investigator of this study, is also willing to talk about any of your concerns with the study at telephone number ( ).

COPY OF CONSENT

If you agree to have your child take part in this research study, you will receive a signed copy of this consent form.

PARENT, INVESTIGATOR AND WITNESS SIGNATURES

"I have read all of the consent form. I have been given a chance to ask questions and have received answers about areas I did not understand. I willingly give my consent for my child to join this study.

_____ I choose to have my child participate in the "passive follow-up" group.

Initials

_____ I choose to have my child participate in the "active follow-up" group.

I understand that I may withdraw my child from the study, should I so desire and that in so doing, I will in no way hurt my child's ongoing medical care at this medical center or elsewhere."

_____		_____	
Child's name	(Date)	Signature of parent or legal guardian	(Date)
_____		_____	
Investigator	(Date)	Signature of parent or legal guardian	(Date)

PEDIATRIC PHASE III CLINICAL TRIAL (BABY HUG)
FOLLOW-UP STUDY

CHAPTER 4

STUDY ENDPOINTS

4.1 INTRODUCTION

The primary objective of the follow-up study is to monitor the continued safety and efficacy of HU treatment during the BABY HUG treatment study in the prevention of splenic and renal injury. Secondary endpoints include evaluation of hematological parameters, measures of renal and splenic function and evaluation of growth and neuropsychological development. The follow-up study will provide additional data for these primary and secondary endpoints for at least two years after the child's participation in the BABY HUG treatment study. The fact that some patients will be on open-label HU during follow-up will allow the assessment of the effects of early, late and continuous treatment with HU.

4.2 PRIMARY ENDPOINTS

4.2.1 Spleen Scintigraphy

Liver-spleen scan will be performed after two years of additional follow-up. The results of this scan will be compared to the two scans performed at initial screening and completion of the BABY HUG treatment study. Thus, pre-treatment, post-treatment and follow-up scans performed at time zero, two and four years respectively will be available for review and comparison. The follow-up scan will be categorized by the same panel of nuclear medicine specialists who read the previous scans. Once again they will be blinded to treatment assignment and not be involved in the acquisition of the images.

4.2.2 Kidney-Glomerular Filtration Rate (GFR)

GFR will be assessed in 3 ways during the follow-up period. Measurement of the GFR will be determined by the performance of a DTPA clearance study four years after the child's enrollment in the BABY HUG treatment study. The results of this measurement will be

compared to previous measurements of the GFR made by DTPA clearance studies done at the initiation and completion of the BABY HUG treatment study. This will give an assessment of the rate of change in GFR and the effects of HU on that change over a four-year period that includes points along the combined continuum of treatment and follow-up studies at times zero, two and four years.

Central laboratory measurement of serum creatinine will be performed once at four years after the child's enrollment in the BABY HUG treatment study. This will be used to estimate the GFR according to the Schwartz formula, GFR=kL/Pcr, where L = the body length in centimeters, Pcr = the plasma creatinine concentration in mg/dl, and k = 0.55 mg creatinine/100 min x cm x 1.73 m^2.

Measurement of Cystatin C will be performed at the Clinical Chemistry Laboratory at St. Jude's and will also be performed once at four years after the child's enrollment in the BABY HUG treatment study. This will also be used to estimate the GFR.

4.3 SECONDARY AND SAFETY ENDPOINTS

4.3.1 Hematologic Parameters

Patients on passive follow-up will have a CBC done at each clinic visit and those patients on open label HU will have additional laboratory monitoring in accordance with routine local clinical care.

Patients on active follow-up will have a local CBC done at each regular clinic visit and those on open label HU will also have a fetal hemoglobin level measured. Patients in the active follow-up group who are not on open label HU will have HbF measured during scheduled visits as noted in Appendix A. They will be compared to pretreatment and treatment levels during BABY HUG. The hemoglobin and mean corpuscular volume (MCV) will be evaluated based on the child's comparison group.

4.3.2 Spleen

Serial pitted red cell counts and quantitation of Howell-Jolly bodies will be performed once, four years after the child's enrollment in the BABY HUG treatment study. The results of the pitted red cell counts will be compared with those performed during the BABY HUG treatment study at screening, 6, 12, 18 months and at completion. This will provide an assessment of changes that have occurred over a four-year period along the combined continuum of treatment and follow-up studies that includes points at times zero, 6, 12, 18, 24 and 48 months. The results for the Howell-Jolly bodies will be compared with those performed at screening and completion of the BABY HUG study. This will provide an assessment of changes that have occurred over a four-year period along the combined continuum of treatment and follow-up studies that include points at times zero, 24 and 48 months.

4.3.3 Kidney Function

Urinary concentrating ability will be measured once, four years after the child's enrollment in the BABY HUG treatment study. The results of these measurements will be compared to the measurements made at screening and completion of the BABY HUG treatment study. This will provide an assessment of the rate of decline in renal papillary function over a four-year period that includes points along the combined continuum of treatment and follow-up studies at times zero, two and four years.

4.3.4 Central Nervous System

Evaluation of the cerebrovascular circulation will be done by TCD performed at 3 years and 4 years after the child's enrollment in the BABY HUG treatment study. The results of these measurements will be compared to the studies performed at screening and completion of the BABY HUG treatment study. This will provide an assessment of the changes that have occurred over a four-year period along the combined continuum of treatment and follow-up studies that includes points at times zero, two, three and four years.

Neuropsychological evaluation with the WPPSI test will be performed once, four years after the child's enrollment in the BABY HUG treatment study. These test results will be compared with the Bayley and Vineland tests performed during the BABY HUG treatment study at screening, 12 months and at completion. This will provide an assessment of changes that have occurred over a 4-year period along the combined continuum of treatment and follow-up studies that includes points at times zero, 12, 24 and 48 months.

4.3.5 Safety Endpoints and Clinical Events

Patients treated with open-label HU will be monitored locally for bone marrow depression with complete blood counts as needed consistent with local clinical standards. Other adverse reactions and toxicity associated with HU treatment will be recorded at each visit.

All patients will be monitored for the occurrence and severity of clinical events. These will be identified by asking standardized history questions at each clinical visit. At each visit, parents will be asked to describe any illnesses experienced since the last visit. If illness is reported, a directed history will be obtained to allow its characterization. Only serious adverse events will be collected in the follow-up study. These are listed in Table 4.2. They will be reported on adverse event (AE) forms to the MCC within seven days. Documentation (discharge summaries, clinic/emergency department records, local laboratory values or radiology reports) for all fatal or life threatening events will be collected by Clinical Center staff for review. Life threatening events include, but are not limited to, bacteremia, meningitis, osteomyelitis, and any event for which the patient receives a transfusion or undergoes surgery. Selected events and supporting documentation collected by Clinical Center staff will be reviewed centrally by two pediatric hematologists who are not a part of the BABY HUG Clinical Center.