

**Pediatric Hydroxyurea Phase III Clinical Trial
(a randomized double blind placebo controlled trial of
hydroxyurea therapy in very young children)**

**INFORMED CONSENT FOR CHILDREN TO JOIN
THE BABY HUG STUDY**

PURPOSE, PROCEDURES AND LENGTH OF STUDY

Your child has sickle cell anemia. This is a blood problem due to a gene that makes your child's red blood cells change shape instead of staying round when the blood oxygen level is low. Red blood cells carry oxygen from the lungs to the rest of the body. Sickle shaped red blood cells can clog the blood vessels, keeping parts of your child's body from getting enough oxygen. Clogs of sickle shaped cells can lead to pain crisis, lung disease, heart failure, stroke and blood stream infection. Some children with sickle cell anemia have few or none of these problems. Some have more than one problem. There is no way to be sure who will have these problems. Sickle cells can hurt any organ in the body. This organ damage can last the rest of your child's life. At present there is no simple treatment that is proven to be safe and to prevent severe harm to organs in young children with sickle cell anemia. The only treatments that are given to almost all children with sickle cell anemia are pain medications and fluids to treat pain crises, and antibiotics for infections. Doctors use blood transfusions for bad problems like sudden swelling of the spleen, stroke, severe lung disease or very low blood counts. Normal stem cells from bone marrow transplant or newborn cord blood are the only treatment that can cure sickle cell anemia. Most children cannot have this treatment because they do not have a matching stem cell donor.

You are being asked to let your child join a research study (called BABY HUG) to test if the use of a drug called hydroxyurea (HU) in children with sickle cell anemia can prevent organ damage. This drug may increase the amount of fetal hemoglobin (the most common protein to carry oxygen in your child's red blood cells at birth) in your child's red blood cells. Fetal hemoglobin may reduce sickling of the red blood cells. The U.S. Food and Drug Administration

(FDA) has approved HU for use in adults with sickle cell anemia but has not approved HU for children, infants or toddlers with sickle cell anemia. Adult patients and children older than five years who are treated with HU do not have as many pain crises as patients who are not treated. So far, only a few infants and toddlers have taken HU as part of a research study. The BABY HUG study will test HU in babies with sickle cell anemia to see if it can prevent damage in the spleen and kidneys. HU has been used for more than fifty years to treat patients with cancer. Lower doses of HU are given for sickle cell anemia. The side effects of HU at dose levels for treating sickle cell anemia are less severe than at dose levels for treating cancer.

The BABY HUG study is being done at University Medical Centers across the country chosen by the National Heart, Lung, and Blood Institute of the National Institutes of Health (the NIH), Bethesda, Maryland.

If you agree, your child will be assigned by random number (like flipping a coin) to one of two groups of patients. One group will receive HU and the other group will receive a placebo (a look alike that has no treatment action). The study must use a placebo in half of the patients to be sure what the results of HU treatment are. You, your child, your doctor, and your study nurse will not know which of the two treatments -- HU or placebo -- your child gets during the study. Your child will have an equal ("fifty-fifty") chance of getting either treatment.

Your child is one of 200 to join this study. Unless the study stops while your child is in the study, your child will take the study treatment for two years. Your child's participation in the BABY HUG study will last for two years. The full study of 200 children will take about four to five years. If there are any problems such as bad effects of treatment that make us want to stop the study, we will let you know when we decide to stop the study, and we will explain the reasons. If the results show that HU prevents organ damage before the study is over, the study will stop early, and we will tell you about the results. You should enroll your child only if you think you and your child will be able to stay with the study for two years.

Two years after joining the study, your child will stop taking study treatment and return to the same care as other children with sickle cell anemia. After your child ends study treatment, we will ask for your family's agreement to make clinic visits every year for approximately five years. We will ask your permission in this long-term follow-up to repeat some of the tests done during the study. You may accept or decline any test and still remain in the long-term follow-up. We plan to tell you the results of the research study after the last child completes study treatment about four to five years from now. Also, we will tell you at that time whether your child received HU or placebo. We do not plan to tell you your child's study treatment assignment or the results of the study before the last child's treatment is over. We would like to know about your child's growth and health for at least ten years if we can. After BABY HUG is over, we need your permission to keep finding out about your child's growth and health.

STUDY TREATMENT

Both the HU and placebo are liquids that are taken by oral syringe. Your child will take the study medicine once a day every day while in the study. Your child's dose may change, depending on your child's growth, any side effects and other study rules. Once in a while, we will ask you to stop giving your child the study treatment because of your child's lab test results.

You will need to bring your child to a clinic visit every two weeks for a blood test for at least the first two months after your child's study treatment starts. It may take longer than two months to get your child's dose set. After your child's dose is set, you will bring your child for a clinic visit every four weeks for a blood test for the rest of the two years to check the dose and make any changes if they are needed. All children (whether taking HU or placebo) will have changes and stops of study treatment doses during BABY HUG. You must have a telephone where messages can be left. You must tell us if you move or get a new phone number so we can contact you about study treatment.

STUDY TESTS

Study doctors will examine your child and do blood tests to detect and avoid side effects. Your child's study treatment may be temporarily stopped or cut down, based on the test results or any side effects that occur. We will check your child's blood counts and kidney and liver tests. We will do other tests to measure the effect of the drug on your child's red blood cells. No more than 3 teaspoons of blood will be taken at any clinic visit. Over two years, less than one half cup of blood will be collected from your child to do the following tests.

- Complete blood counts.
- Biochemistry panels.
- Sickle cell confirmation test.
- Pitted cell counts to check spleen function.
- Cytogenetics – karyotype and chromosome breakage analyses.
- DNA/VDJ mutation studies to investigate and measure any abnormal changes in the cells that would be a sign of increased risk of blood cancer.
- Immune function studies to determine the effects of hydroxyurea treatment on antibody responses to standard vaccines administered before and during hydroxyurea therapy.
- Assess the levels of study treatment in the blood.

Most clinic visits will last less than half a day. Twice a year, extra tests will make the visit last all day. At the beginning and end of the study, we will do spleen and kidney tests that use radiation to check the results of study treatment, and we will collect your child's urine in a bag for a kidney function test.

All children (whether taking HU or placebo) will have the same tests during BABY HUG. We will get two radiation tests -- one of your child's spleen and another of your child's kidney function -- at the start and end of the study. Each special test takes a visit by itself. For the tests of kidney function and of spleen function, small doses of radioactive material are 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 immediately after the first dose of study treatment. These samples are used for the kidney test and to measure the levels of study treatment in the blood over time.

Approximately one month after your child begins study treatment we will take two blood samples over 90 minutes immediately after administering study treatment dose to further assess the levels of study treatment in the blood.

We will measure your child's weight at every clinic visit (at least 12 times a year). We will measure your child's height and head circumference every three months (at least 4 times a year).

We will use ultrasound or sound waves to check your child's gall bladder and other organs in the abdomen. We will perform these sound wave studies before the start and at the end of your child's participation in the study. We will use a separate sound wave study to check the speed of blood flow in the blood vessels going to your child's brain. We will perform these sound wave studies before the start, at the middle (after one year on study treatment) and at the end of your child's participation in the study.

We will give your child learning tests that will involve asking you questions and watching your child's activities. We will have a neurologist examine your child. We will perform these tests before the start, at the middle and at the end of your child's participation in the study.

A set of the tests for the study – blood tests, radiation tests of the spleen and kidney, ultrasound of the body, a urine test and a learning test – must be complete for study treatment to begin.

We will want to know about every time your child is in the hospital. We will want you to allow us to check your child's records every time your child is in the hospital.

Some of our questions will be about private family concerns such as your jobs, home size or income. The answers to these questions will help us to compare BABY HUG children to children in other studies. You may decline to answer any of these questions and still keep your child in BABY HUG.

RISKS

Any drug may have side effects. The study treatment used in this study may cause some or none of the listed side effects in your child. There is always a small risk of rare or unknown side effects.

HU has several possible side effects. HU can cause the bone marrow to stop making blood cells, but the bone marrow almost always gets better if HU is stopped for two weeks. HU may cause fever, hair loss, nausea and vomiting (less than one in a thousand at the doses used). Rare side effects may include rash or redness of the skin, or even severe sores on the hands (consider wearing gloves when handling HU, and washing hands after), darkening of the skin or nails, headache, dizziness, diarrhea or damage to the liver or kidney (less than one in ten thousand).

Blood cancer has been found in adults who were treated with HU and who had conditions known to lead to blood cancer, and in a very few adult sickle cell anemia patients who were treated with HU. Whether or not HU caused these blood cancers is not known. It is not known if there is any increase of cancer in children who are treated with HU. HU causes birth defects in animals that are given large doses of the drug during pregnancy. It is not known if there is a risk to an unborn human baby. Side effects that we do not know about now might be found out at a later time.

In some baby mice and rats, large doses of HU have kept the body and almost all vital organs from growing as they should. In human babies and toddlers so far, HU has not had this effect on growth at the doses we plan to use.

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 will have one or more medical imaging studies. The tests your child will have include a liver/spleen scan and a DTPA scan. These tests involve a small amount of radiation. To give you an idea about how much radiation your child will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally occurring radioactive forms of water and minerals. This research gives your child the equivalent of about three extra years' worth of this natural radiation. 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.

Your child's name is not linked to any data or specimens and investigators monitor the tests being performed on all specimens to prevent unauthorized use. However, performance of an unauthorized procedure with blood samples collected as part of the research has happened accidentally one time in the study, and there is a small risk it could happen again. If there is an instance in which an unauthorized use of your child's study data or specimens occurs, study staff will notify you as soon as they are aware of such an incident.

SAVED BLOOD

Left-over blood, or other samples taken from your child during this study may help in other research, or in teaching, or in the development of a new product.

You agree

 Initials

that <<insert Clinical Center name>> and

do not agree

members of its staff may use your child's

cells, blood, or other samples for these purposes. We will keep these study samples as long as we can or until the samples are used up. These left over samples cannot be used to take care of your child. When a test is needed a fresh sample must usually be taken.

The samples may be used to study an illness not related to sickle cell anemia.

You agree

Initials

that your child's stored blood samples may

be given to other doctors for use in research

do not agree

in a way that will not allow them to trace the blood

back to your child. Use of DNA from the blood will be strictly private. No facts that could single out your child are given with the DNA. These uses of blood will in no way hurt the study of sickle cell anemia in your child. Any DNA sample from your child will be marked with a code number, and all other facts that could single out your child will be removed. <<Insert Clinical Center name>> will keep a code sheet locked in an office away from the study office. The sheet links the sample code number to your child's name and hospital number. If your child's DNA is found to carry a risk for another disease that we know at the time of testing can shorten life or cause serious problems, we send you a certified letter saying to contact <<insert PI's name>> at <<insert Clinical Center name>>. <<Insert PI's name>>'s staff will not let out any specific facts over the phone or in the mail. Please give us any change in your address, since the letter will be sent to the last address we have for you. The link from the blood sample to your child will be shared only if we are asked for the link under an order of law.

BENEFITS

No one knows whether or not the study treatments will help your child. Your child has an equal chance of receiving HU or placebo. It is possible that your child will not benefit from participation in this study. The results of this study will help doctors decide in the future whether to give HU to very young children with sickle cell anemia. If there are good effects of taking HU, children who get HU in the study may have them.

FREE CHOICE

Joining this study is your free choice for your child. 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 this study is to go on with standard care for sickle cell anemia with your child's doctor. You and your child's doctor could plan to use or not use HU. Some children with sickle cell anemia get other treatments that may be possible for your child instead of this study; these treatments include blood transfusions and bone marrow transplants. Your choice about this study will not change the way your child is treated in our clinic. In or outside the study, we want to give the best care for your child.

COSTS

There will be no extra cost to you for the study. We will give your child study drugs and study tests free of charge. The cost of usual medical care will not be paid by the study. Usual care will be billed, as before, to you or to your third party payer.

PAYMENTS

At each visit, each family with a child in the study at this clinic will receive \$ _____ 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 any one 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 link to your child or family directly. The computer file may be used by other doctors to study sickle cell anemia.

You agree _____ for the data file to include your child. Data may
 do not agree _____ be given to the National Institutes of Health, the Food and Drug Administration or other U.S. or state agency as required.

LIMITS

If the study doctor decides that your child should not be in the study, your child will stop getting study drug, and the schedule of study visits will change for you. The study doctor will explain to you in full the reason for any such change.

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.

The rights of research subjects can be discussed with the Chairman of the University of Medical Center's Institutional Review Board, telephone number () _____.
Dr. _____, Principal Investigator of this study, is also willing to talk about any of your concerns with the study at telephone number _____.

PATIENT/FAMILY ADVOCATE

Before your child joins this study, you should talk this study over with <<insert Patient/Family Advocate name>>, a person who knows about sickle cell problems and the choices you have. This person will give you any help you need to make clear the questions to think about and the answers you need before you can say if this study is right for you and your child. This person is not part of your health care team or of the research team. He/She can talk freely with you about all your concerns for the study.

COPY OF CONSENT

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

SIGNATURE OF PATIENT/FAMILY ADVOCATE

_____ has/have been given a chance to ask questions and talk with me about BABY HUG. They are well informed to freely give consent and understand that they may withdraw from the study should they so desire.

Patient/Family Advocate Signature

Witness (Date)

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 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)

Person obtaining consent (Date)

Witness (Date)