

APPENDIX B

CONSENT AND ASSENT FORMS

Informed Consent to Participate in Research

Unrelated Donor Reduced Intensity Bone Marrow Transplant for Children with Severe Sickle Cell Disease

This is a clinical trial, which is a research study to answer specific medical questions. The information from this study may also help future patients. The Study doctor (the person in charge of the research) will explain the study to you and your child. This research study will include only people who choose to take part. Please take your time to make your decision about allowing your child to take part. You may discuss your decision with family and friends. You and your child should also discuss this with your child's health care team. If you, or your child, have any questions, you and your child can ask the Study doctor for more explanation.

This is a consent for a research study. Your child is being invited to participate in this study because your child has severe sickle cell disease that may be treated with a bone marrow transplant. This form is intended to give you and your child information to help you decide if you and your child want to participate in this study. You should read this form and ask any questions you or your child may have before agreeing to be in the study.

Children with sickle cell disease are born with a defect in hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen to vital organs such as the brain, heart, lungs and kidneys. Defective hemoglobin damages red blood cells and makes them sticky. This causes them to look like a sickle. The damaged or sickled red blood cells can block blood flow in blood vessels and block oxygen and nutrients from reaching organs. As a result almost all the organs in the body can be damaged but it is especially bad when vital organs are involved. When the flow of blood is blocked in a blood vessel in the brain, a stroke occurs. When blood flow is blocked in a bone or muscle, this causes severe pain. If it occurs in the lung, this complication is called acute chest syndrome and causes chest pain and a low oxygen level. Sickle cell disease can also cause anemia.

It is possible to replace the defective red blood cells with normal blood cells in children with severe sickle cell disease by performing a bone marrow transplant. We know this from recent studies where bone marrow from a brother or sister has replaced the defective sickled red cells after transplantation. Blood vessels are no longer blocked, and the anemia goes away.

However, a bone marrow transplant is an intensive medical procedure and there are serious risks involved. Therefore, it is usually offered only to children who have had severe complications of sickle cell disease such as stroke, frequent painful crises, or repeated episodes of acute chest syndrome. In most cases, it is offered only to children who have a healthy brother or sister who

is HLA-identical, which means that the donor has the same ‘tissue’ type as the person receiving the transplant.

Most children with severe sickle cell disease do not receive a transplant because they do not have the same tissue type as their healthy brothers or sisters. These children are often treated with medicines and regular red blood cell transfusions for many years to try to control symptoms and organ damage. However, in children with sickle cell disease who have had a stroke, 20% (1 in 5) will develop a second stroke and, of that group, 30% (1 in 3) children will develop a third stroke even if they are receiving regular blood transfusions.

Cells in the bone marrow that make healthy red cells are called blood stem cells.

This study is a clinical trial for children with severe sickle cell disease that do not have a brother or sister with the same tissue type who can serve as their donor. Although previous studies have shown that a bone marrow transplant is possible for patients with a healthy related bone marrow donor, this study will determine if this is a good treatment option for patients transplanted with cells from an unrelated donor. Patients who participate in this study will also receive lower intensity treatment (conditioning) before transplant with bone marrow donated by a healthy adult donor.

This lowered intensity conditioning treatment (reduced intensity conditioning regimen – RIC) is being used to decrease the side effects or toxicities of the conditioning treatment. It is not known whether this RIC will be successful in allowing donor cells to settle in the patient and grow successfully. This is the research question that is being asked in this study.

Before you decide whether or not to have your child join the study, please read all the information in this consent form. Feel free to ask questions to understand your child’s rights and protections. The choice to take part in this study is completely voluntary.

Sponsor and source of funding:

This study is sponsored by the National Institutes of Health (NIH) and the National Marrow Donor Program® who is the primary source of funding. Additional NIH sponsors include the Sickle Cell Disease Clinical Research Network (SCD-CRN) and the National Center on Minority Health and Health Disparities. The NIH is a government program that funds the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), a group of transplant programs conducting research in transplantation for several diseases including severe sickle cell disease.

If you decide to allow your child to take part in this research study:

- You or your child's insurance company will be responsible for all medical bills from your child's transplant.
- You or your child will not pay for any extra tests that are being done for the study (these are lab tests, scans and other special tests that are not part of regular, routine care). The extra research tests that are being done for this study are a blood test to measure function of the spleen, a special scan of the brain called an MRA/MRI (magnetic resonance angiography and imaging after injection of contrast), measurement of brain function using performance tests that are age-dependent, and question sheets that measure quality of life. The tests that measure learning and brain function will be done before transplant and again 2 years after transplant. Quality of Life question/answer sheets will be completed before transplant and at 3, 6, 12 and 24 months after transplant.
- You or your child will not be paid to take part in this study.

If you decide not to allow your child to participate in this study, your child's study doctor will discuss other treatment options with you.

What other choices does your child have if your child does not take part in the study?

Your child's other choices may include:

- Treatment with drugs such as hydroxyurea that may lessen complications of severe sickle cell disease.
- Experimental treatments with new drugs for severe sickle cell disease.
- A transplant using bone marrow without being part of this study where the choice of medicines before and after transplant, and other guidelines may be different.
- Other treatments such as regular RBC transfusions to try to control symptoms related to your child's severe sickle cell disease. However, **RBC transfusion therapy may not prevent further strokes in all children who have had an initial stroke.**

It is important that you talk to your child's study doctor about your child's treatment choices before you decide to have your child participate in this study.

Why is this study being done?

This study is being done to determine if blood cell transplants, with bone marrow from unrelated donors, are effective in children with severe sickle cell disease and if this treatment approach has acceptable risks and side effects. The study will also look into the risk of death associated with this treatment approach and if it is acceptable considering the potential benefit of avoiding the long-term consequences of severe sickle cell disease. Transplant studies for sickle cell disease have previously used high dose chemotherapy to prepare patients for transplant (myeloblastic conditioning). This has been successful mostly in patients who had tissue-matched family members such as brothers or sisters, as donors. In this study, the success of transplant for sickle cell disease is being measured after using reduced intensity conditioning treatment to reduce toxicities of treatment using tissue-matched unrelated donor cells. This is being done to try to avoid the toxicities of more intense conditioning treatment.

This research study is being done to answer the following questions:

- Is it safe to transplant children who have severe sickle cell disease with bone marrow from a healthy, unrelated donor?
- Are the drugs given to patients in this study (reduced intensity conditioning) effective in destroying sickle cells and allowing blood cells from a healthy donor to grow in the recipient?
- After transplant, will children with sickle cell disease make healthy red blood cells and avoid the health problems caused by sickle cell disease?
- After transplant, will children with sickle cell disease experience any side effects that shorten their life or worsen their quality of life?

How many children will take part in the study?

Thirty (30) children in the U.S. will take part in this study. To be part of the study your child must:

- Be between the ages of 3 and 19 years
- Have severe sickle cell disease with one or more of the following sickle cell complications:
 - Stroke or other severe sickle cell disease complication affecting the brain
 - Repeated acute chest syndrome episodes, despite treatment
 - Repeated severe pain episodes despite treatment
- Not have a healthy brother or sister who has the same tissue type who is able and willing to donate
- Have an acceptable unrelated marrow donor available
- Provide a signed consent for participation in the study (your child signs an assent form if they are old enough to understand the risks and benefits)

What will happen if your child takes part in this research study?

Before the transplant:

The first step in considering your child for an unrelated blood or marrow transplant is to have an eligibility review panel (a group of 5 sickle cell disease experts and blood and marrow transplant physicians unconnected with this trial) review your child's medical history. Once they have confirmed that your child is eligible for this trial we will proceed with the pre-transplant work-up and research tests listed below. In the unlikely event that they determine that your child is not eligible for this trial, your doctor will discuss other transplant and treatment options with you.

The following research tests will be performed:

- Question/answer sheets to measure quality of life before transplant.
- Pitted red cell count before transplant to measure spleen function which is decreased by sickle cell disease.
- Special tests of learning and brain function called 'Neurocognitive testing'. These tests are done to learn about any effects of sickle cell disease on brain function before the transplant, and compare 2 years after transplant to see if there is a change.
- MRA and MRI tests before transplant will be performed as part of the research for this study.

These tests will be done as an outpatient before the transplant over the course of several days.

To help with the administration of medicines, blood transfusions and obtaining blood for lab tests, a central venous catheter (also known as a ‘Hickman’ or ‘Broviac’ catheter) will be placed before the transplant. This is a hollow tube that is inserted by a surgeon or radiologist usually in the operating room. The doctor performing the procedure will explain it in more detail before the procedure. Your child’s anesthesiologist will describe the risks of a general anesthetic. The tube is placed in the chest and allows medicines, transfusions, etc. to be given painlessly into the vein without the need for repeated sticking of needles in your child’s arms. Once the central venous catheter is placed, it will need daily care at home with cleaning and injection of medications to prevent catheter-related blood clots.

Transplant/conditioning:

Conditioning is the chemotherapy and other medicines given to prepare your child to receive donor cells. It prevents your child’s immune system from rejecting donor cells. Conditioning will start 22 days before transplant.

The medicines used are alemtuzumab, fludarabine, and melphalan. Alemtuzumab will be given intravenously (through your child’s central venous catheter) once a day for 3 days (after a small test dose) beginning 3 weeks before the transplant. The test dose is given to make sure that your child will not have a bad reaction to the full dose. If your child has a bad reaction, your doctor will discuss the best way to proceed. Your child will be admitted during alemtuzumab infusions and may be discharged if well the day after the infusions are completed.

Next, your child will return to the hospital for admission to the bone marrow transplant unit to receive fludarabine and melphalan starting 8 days before the transplant. Fludarabine will be given intravenously once a day for 5 days. Finally, melphalan will be given intravenously 3 days before the transplant. This will be followed by 2 “rest days” when your child will not receive any chemotherapy.

| Day | Treatment |
|---|---|
| 24 hours before 1 st dose of Alemtuzumab | Alemtuzumab test dose |
| 21 days before transplant 20 days before transplant 19 days before transplant | Alemtuzumab Alemtuzumab Alemtuzumab |
| 8 days before transplant | Fludarabine |
| 7 days before transplant | Fludarabine |
| 6 days before transplant | Fludarabine |
| 5 days before transplant | Fludarabine |
| 4 days before transplant | Fludarabine |
| 3 days before transplant | Melphalan |
| 2 days before transplant | Rest |
| 1 day before transplant | Rest |
| Transplant day | Bone marrow infusion |

Bone marrow transplant:

Your child will be given the marrow transplant on Day 0. The donated marrow will come from a suitably tissue-matched unrelated person. The donor cells will be given through the central venous catheter, in a manner similar to a blood transfusion.

Immunosuppression to prevent graft-versus-host disease (GVHD):

Three days before the transplant, your child will begin to receive medicines to hold back the immune system and these medicines will continue after the transplant. This may make your child develop more infections than usual. However, these drugs are important to allow donor cells to accept their new role and to lower the chance of their injuring your child's organs by causing graft-versus-host disease (GVHD). GVHD is an attack by the donor cells against your child's body. GVHD is discussed in greater detail below. Your child will receive one or more standard drugs to prevent GVHD and these will be given for at least 6 months after the transplant. These drugs include tacrolimus (also called FK 506 or Prograf®), methylprednisolone or prednisone, methotrexate, and cyclosporine (also called Gengraf® or Neoral®) and may be used in different combinations. Choice of drugs may depend on the preference of the transplant team at your hospital.

Post-transplant follow-up and care:

The conditioning regimen will destroy your child's blood and marrow cells. This will cause low counts of white blood cells, red blood cells, and platelets. Blood stem cells from the donor will produce new blood cells to replace the destroyed recipient cells. To speed this process along after the transplant, your child will receive granulocyte-colony-stimulating factor (also called G-CSF or Neupogen). G-CSF is a natural protein made in the body that increases the white blood cell count and that is used to help protect against infections. Your child will start receiving G-CSF one week after the transplant. It is given either by injection under the skin or intravenously. Your child will receive it daily until the white blood cell count has recovered.

Your child will stay in the hospital after the transplant until the doctor feels it is safe for your child to go home. During that time, your child will be carefully watched for signs of infection and other problems. A physical exam and blood tests will be done daily. Additional blood tests, medications, and procedures may be required if problems arise.

After leaving the hospital, your child will need to visit the transplant clinic at least once a week for check-ups, blood counts, and chemistries to make sure that he/she is doing well medically. Eventually the visits will be less frequent. Your child will be examined at 100 days, 6 months, 1 year and 2 years after transplant to check your child's progress and treat any problems. The following tests will be performed during these visits:

CLINICAL TESTS

| Test | Purpose | When Performed |
|---|---|--|
| Blood Tests (1-3 tablespoons or 10-30 ml) | Check number of donor cells in your child, hemoglobin level, and recovery of immunity | 28 days, 42 days, 100 days, 180 days, one year, and two years after transplant |
| Lung and Heart Function | Check the health of heart and lungs | One year and two years after transplant |

TESTS FOR RESEARCH

| Test | Purpose | When Performed |
|-------------------------------|---|--|
| MRA/MRI Scan | Check structure and flow of blood vessels in the brain | 2 years after transplant |
| Neurocognitive Testing | Detect any changes in memory and learning abilities | 2 years after transplant |
| Quality of Life Questionnaire | Check child's quality of life compared to before transplant | Before transplant, and 100 days, six months, one year and two years after transplant |

You may decide to take your child out of any research test at any time.

In addition to these, your doctor will decide if other tests and treatments that are not part of this research study are necessary for good medical care.

How long will your child be in the study?

Your child will be in the study for 2 years. Please notify your child's transplant doctor if you move or change your child's primary care doctor so that we will be able to obtain all the necessary information about your child's health.

Can your child stop being in the study?

You can decide to stop your child's participation at any time. Tell your child's doctor if you or your child are thinking about stopping or decide to stop. The doctor will tell you and your child how to stop safely. It is important to note that once your child receives the medicines for the conditioning regimen, he/she must receive the unrelated donor marrow in order for the blood counts to recover in a timely fashion.

If you decide to withdraw your child, or your child's doctor withdraws your child from the study, we will ask your permission to use all the information about your child that has already been collected as part of the study. We will also ask your permission to continue to allow your child's doctor to tell us about his/her progress until at least two years post-transplant. You can choose to give or not to give this permission.

Can the doctor who is the Principal Investigator withdraw your child from this study?

Your child can be taken off the study (with or without your consent) for any of the following reasons:

- Your child needs a medical treatment not allowed in this study
- The investigator decides that continuing in the study would be harmful to your child
- Your child becomes pregnant and the study treatment could be harmful to the fetus
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH)

What are the risks of being in this study?

Catheter placement: Pain at insertion site, minor bleeding and infection may happen. Rare side effects associated with this procedure include lung puncture and severe bleeding. A chest X-ray or CT scan will be obtained to confirm the catheter location before it is used for the first time.

POTENTIAL SIDE EFFECTS OF STUDY DRUGS

The most common side effects of the treatments to be used in this study are listed below. There is also the risk of very uncommon or previously unknown side effects.

Alemtuzumab

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|--|---|---|
| <ul style="list-style-type: none"> • Fever • Chills • Anemia due to decreased number of red cells • Infection due to decreased number of white blood cells • Bleeding due to decreased numbers of platelets • Weakened immune system | <ul style="list-style-type: none"> • Nausea • Vomiting • Diarrhea • Rash • Headache • Sweating • Back pain • Severe itching • Allergic reaction of skin and blood vessels • Tiredness • Loss of appetite | <ul style="list-style-type: none"> • Abdominal pain • Dizziness • High blood pressure • Blisters • Pain in the muscles • Herpes simplex infection • Inflammation of the throat |

Fludarabine

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|--|--|---|
| <ul style="list-style-type: none"> • Anemia due to decreased number of red cells • Infection due to decreased number of white blood cells • Bleeding due to decreased numbers of platelets • Tiredness • Nausea • Vomiting • Weakened immune system | <ul style="list-style-type: none"> • Pneumonia • Diarrhea • Mouth sores • Skin rash • Fever • Swelling of hands and feet | <ul style="list-style-type: none"> • Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet • Changes in vision • Agitation/nervousness • Confusion • Cough • Difficulty breathing • Weakness • Severe brain injury and death |

Melphalan

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|---|---|--|
| <ul style="list-style-type: none"> • Loss of appetite • Nausea • Vomiting • Skin breakdown if drug leaks from vein • Anemia due to decreased number of red cells • Infection due to decreased number of white blood cells • Bleeding due to decreased numbers of platelets • Mouth sores • Temporary hair loss | <ul style="list-style-type: none"> • Diarrhea • Inflammation of the lung • Weakness • Weight loss | <ul style="list-style-type: none"> • Low blood pressure • Excessive perspiration • Allergic reaction • Damage/ scarring of lung tissue • Sterility • Seizure |

G-CSF (Filgrastim)

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|--|--|--|
| | <ul style="list-style-type: none"> • Local irritation (skin) at injection site • Ache or pain inside the bones. Increased levels of liver enzymes and uric acid in the blood • Bleeding due to decreased numbers of platelets | <ul style="list-style-type: none"> • Allergic reaction, low fever • Enlargement or rupture of the spleen • Worsening of pre-existing skin rashes • Temporary hair loss • Inflammation of a blood vessel in the skin |

Potential Risk of RPLS/PRES

The Data Safety and Monitoring Board (DSMB) of the Blood and Marrow Transplant Clinical Trials Network is a group of transplant, sickle cell disease and other experts that ensure the safety of patients treated on this and other trials. This group carefully monitors the experience of patients to make sure that the side effects that they experience are not unusual or more frequent or more severe than would be expected.

The DSMB has noted that children transplanted on the clinical trial BMT CTN 0601 have a higher than expected occurrence of a usually uncommon (< 5%) complication called reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES). Patients with RPLS/PRES have confusion and other changes in their ability to think. Sometimes, they experience seizures, sleepiness or, rarely, loss of consciousness. RPLS is diagnosed with an MRI of the brain. It is a disorder that is sometimes seen in patients with sickle cell disease even if they do not have a transplant. In transplant patients, it is usually caused by some of the drugs used to prevent or treat graft versus host disease. It can often, but not always, be prevented by very careful control of blood pressure. It is treated by changing graft versus host disease drugs, controlling blood pressure and/or giving anti-seizure medicines. About a quarter of the patients on BMT CTN 0601 have developed RPLS/PRES; all were successfully treated for this complication. Thus far, no RPLS/PRES has been observed in any patient more than 6 months from their date of transplant. We believe that children who are on prednisone or other corticosteroids, or immunosuppressive drugs such as cyclosporine or tacrolimus or have high blood pressure are more likely to develop RPLS/PRES.

If your child experiences any of these side effects or changes in mental status, you should contact your child's transplant physician right away, since early treatment is important. It is also important that any blood pressure medication be taken as prescribed to decrease the risk of RPLS/PRES.

RISKS AND TOXICITIES RELATED TO STANDARD TRANSPLANT PROCEDURES

Graft-versus-Host Disease (GVHD): This condition results from white cells called T cells in the donor's bone marrow cells recognizing your child's body as foreign and attacking it. Your child is more likely to get GVHD if the donor's tissue type does not match your child's tissue type well.

There are two forms of GVHD: acute GVHD (usually occurs in the first 3 months after transplant) and chronic GVHD (usually occurs later and lasts longer). Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened skin, joint stiffness, dry eyes, dry mouth, liver disease, weight loss, diarrhea and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, your child may be asked to have a skin biopsy (i.e., taking a small sample of skin tissue to look at under the microscope) and possibly an intestinal biopsy and rarely a liver biopsy.

There is a 10-20% chance that your child will develop GVHD after the transplant. Your child will be watched closely for this complication and given treatment to treat it further if it occurs despite the medicines given to prevent it. In most cases, GVHD can be successfully treated. If GVHD does not respond to the medicines listed above, treatment can involve combinations of many other medicines with different side effects. Treatment may be necessary for many years as GVHD symptoms can last for many months or years. Prolonged treatment for chronic GVHD can result in a weak immune system and infections and may need frequent medical care and hospitalization. Sometimes GVHD is severe or difficult to treat and may lead to death.

SIDE EFFECTS OF MEDICINES USED TO PREVENT GVHD

The side effects listed below are usually reversible once the medicines are discontinued.

Cyclosporine: This drug may be used for all patients.

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|---|--|--|
| <ul style="list-style-type: none"> • High blood pressure • Kidney problems • Headaches • Nausea • Vomiting • Stomach pain or indigestion • Swelling of the hands or feet | <ul style="list-style-type: none"> • Tremors • Increased hair growth | <ul style="list-style-type: none"> • Muscle cramps • Numbness and tingling of the hands or feet • Seizure |

Tacrolimus: This drug may be used for all patients.

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|---|---|---|
| <ul style="list-style-type: none"> • Anemia • Loss of appetite • Diarrhea • High potassium levels • High blood pressure • Nausea • Fever • Headache • High blood sugar | <ul style="list-style-type: none"> • Hair loss • Vomiting • Tingling sensation in the extremities • Itching • Rash • Abdominal pain | <ul style="list-style-type: none"> • Confusion • Painful joints • Increased sensitivity to light • Blurred vision • Insomnia • Infection • Jaundice • Kidney injury • Seizures |

Methotrexate: This drug will be used as part of GVHD prophylaxis Regimen 1 for bone marrow recipients.

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|--|--|---|
| <ul style="list-style-type: none"> • High levels of liver enzymes | <ul style="list-style-type: none"> • Nausea • Vomiting • Loss of appetite • Diarrhea • Mouth sores • Sensitivity to sunlight • Increased risk of sunburn • Decreased number of red and white blood cells and platelets | <ul style="list-style-type: none"> • Hair loss • Dizziness • Redness, tenderness, darkening, and peeling of skin • Blurred vision • Allergic reaction • Damage to nerve tissue • Kidney damage • Seizures • Decreased lung function • Decreased liver function - temporary • Bone and tissue damage • Loss of memory, concentration, balance, and walking • Poor nervous system function |

Methylprednisolone: This drug will be used as part of GVHD prophylaxis Regimen 1 for bone marrow recipients.

| Likely <i>("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)</i> | Less Likely <i>("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)</i> | Rare, but Serious <i>(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)</i> |
|--|--|---|
| <ul style="list-style-type: none"> • Water retention • Overeating • Weakened immune system • Temporary personality changes • Abnormal hormone production • High blood sugar • Slowed growth • Decreased bone density | <ul style="list-style-type: none"> • Headaches • Poor wound healing • Stomach swelling or pain • Tissue swelling • High blood pressure • Stomach ulcer • Muscle weakness • Cataracts | <ul style="list-style-type: none"> • Difficulty in falling asleep • Worsening of diabetes • Inflammation of pancreas • Personality disturbances • Bleeding in the stomach and intestines • Increased pressure within the eye • Disturbance of bone calcium which can lead to possible fractures or permanent bone damage |

Damage to the vital organs in your body. The conditioning or GVHD treatment could result in problems in the heart, lungs, liver, intestine, kidneys and bladder, brain etc. Lung problems can be the result of infections or chemotherapy. Some patients can have veno-occlusive disease of the liver (VOD). This complication usually results from high doses of chemotherapy. Patients with VOD become jaundiced (yellowish skin), have liver function abnormalities, fluid retention, abdominal swelling, and abdominal pain. If organ damage symptoms are severe, your child may have to stay in the hospital longer or be re-hospitalized after transplant. Although many patients recover completely, these complications may cause permanent damage or even death.

Serious infections. Full and complete recovery of your child's immune system may take many months following the initial recovery of your child's cell counts. During this time, there is an increased risk of infections. Your child will be prescribed certain medications to reduce the chance of those infections. However, preventive treatments are not always effective. If your child has an infection, he/she may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections are fatal.

Recurrence of disease and graft rejection. Since the study uses a conditioning treatment regimen of reduced intensity, it may not allow donor cells to grow and your child may partially or fully reject the donor's bone marrow. If this happens, your child's blood cells will grow back again and the severe sickle cell disease may persist or come back even if the transplant is initially successful.

Central venous catheter complications. The most common complications associated with central venous catheters are blood clots in the catheter and infection. If clots form, a medicine will be injected to dissolve the clot. If it cannot dissolve, the catheter may need to be replaced. Infections will be treated with medicines; sometimes, removal of the infected catheter is required and a new catheter will need to be placed.

Impact on reproductive hormone function and sexuality. High doses of chemotherapy can cause sterility (inability to have children) and decreased hormone levels. Some patients with chronic GVHD have reported impaired sexual function due to decreased sexual desire and vaginal dryness. Since the chemotherapy doses used in the preparative regimen for this study are lower, the risk of sterility may be lower. Some patients treated with this preparative regimen have had children after their transplant. However, it is difficult to know the exact risk of sterility after transplant with the use of this conditioning regimen.

Risk of death. Some of the side effects of an unrelated donor transplant may be very severe and may cause death of the recipient despite using all supportive care. Though all precautions will be taken to make the transplant as safe as possible for your child, there is still a 10% chance of the patient's death following unrelated donor transplantation.

Quality of life surveys. Completion of the quality of life surveys will not cause you or your child any physical discomfort, although it is possible that you or your child will find some of the questions or topics upsetting. You or your child may experience emotional distress or feel a loss of privacy. If you do, there will be someone available to speak with you and your child. They will be able to refer you to appropriate counselors or other support people.

Are there benefits to taking part in the study?

Your child may or may not benefit from taking part in this study. If the transplant is successful, your child may benefit by not having further symptoms and complications of severe sickle cell disease. The information obtained from your child's participation in this study will help doctors treat future patients with severe sickle cell disease who require a transplant using unrelated donor bone marrow.

What are the costs of taking part in this study?

Most of the care given in this study is standard care; it will be billed to you or your child's insurer in the usual way. Standard costs include those of your child's hospitalization, doctor's visits, standard laboratory tests, medications, and the cost of the donor's bone marrow. There will be no charge for research tests.

What happens if your child is injured because of participation in this study?

In the event that this research activity results in an injury, treatment will be available, including first-aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to your child's insurance company. If you or your child thinks that your child has suffered a research-related injury, let the study doctors know right away. It is important that you tell your child's doctor, _____ [investigator's name], if you or your child feel that your child has been injured because of taking part in this study. You can

tell the doctor in person or call him/her at _____ [telephone number]. Your child will receive medical treatment if injured as a result of taking part in this study. You or your child's insurance will be charged for this treatment.

What are your child's rights if your child takes part in this study?

You may choose to allow your child to either take part or to not take part in the study. If you decide to allow your child to take part in this study, your child may leave the study at any time. No matter what decision is made, there will be no penalty and your child will not lose any of his or her regular benefits. If your child leaves the study, he/she can still get medical care from your child's doctor and transplant center. We will tell you and your child about new information or changes in the study that may affect your child's health or your willingness to continue in the study. In the case of injury resulting from this study, your child does not lose any legal rights to seek payment by signing this form.

Who can answer your and your child's questions about the study?

You and your child can talk to your child's doctor about any questions or concerns about this study. Contact your child's doctor _____ [name(s)] at _____ [telephone number].

For questions about your child's rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your child's rights) at _____ (telephone number).

Will your child's medical information be kept private?

We will do our best to make sure that the personal information in your child's medical record be kept private. However, we cannot guarantee total privacy. Your child's personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your child's name and other personal information will not be used.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Organizations that may look at and/or copy your child's medical records and protected health information for research, quality assurance, and data analysis include:

- Members of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), which is conducting this study
- The EMMES Corporation, a research organization that is helping to coordinate this study
- The National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR), organizations involved in research on blood and marrow transplantation and in the coordination of this study
- The National Heart, Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

- The Sickle Cell Disease Clinical Research Network (SCD CRN)
- Researchers and staff members at Washington University for central review of MRI images

Expiration date for retention of records:

The study results will stay in your child's research record at (*insert Institution*) for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your child's medical record will be destroyed or your child's name and other identifying information will be removed from such study results. Research information in your child's medical record will be kept indefinitely.

How will the researcher(s) benefit from your child being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in the scientific press. In addition, the sponsor (the NIH) is paying the Principal Investigator to conduct this study. The investigators have no financial interest in the drugs used in the study.

HIPAA¹ authorization to use and disclose individual health information for research purposes:

- a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my child's individual health information for the purpose of conducting the research study entitled *Unrelated Donor Hematopoietic Cell Transplantation for Children with Severe Sickle Cell Disease Using a Reduced Intensity Conditioning Regimen*.
- b. Individual Health Information to be Used or Disclosed: My child's individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results). The identities of individuals such as names and addresses will not be shared or de-identified to make sure information cannot be linked to you.
- c. Parties Who May Disclose My Child's Individual Health Information: The researcher and the researcher's staff may obtain my child's (my) individual health information from:
(*list: hospitals, clinics or providers from which health care information can be requested*)

¹ HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

d. Parties Who May Receive or Use My Child's Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by my child during the course of the research may be received and used by the following parties:

- Members of the BMT CTN Data and Coordinating Center and BMT CTN #0601 Protocol Team
 - National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
 - The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research
 - U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
 - U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
 - The Sickle Cell Disease Clinical Research Network (SCD CRN)
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- e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, my child will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.
- f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of the decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about my child (me) will be collected by or disclosed to the researcher for this study.
- g. Potential for Re-disclosure: My child's individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.
- h. This authorization does not have an expiration date. However, you can elect at any time to withdraw your authorization to participate in the study.

You will receive a copy of this form. If you (or your child) need more information about this study, ask the study doctor.

SIGNATURE

I have read the information in this consent form and have had the study explained to me. My questions have been answered to my satisfaction. I agree to allow my child to participate in the study.

Signature of Subject's Mother/Guardian

Date

Printed Name of Subject's Mother/Guardian

Signature of Subject's Father/Guardian

Date

Printed Name of Subject's Father/Guardian

Signature of Patient/Study Subject (if greater than or equal to 18 years of age)

Printed Name of Patient/Study Subject (if greater than or equal to 18 years of age)

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the above individual(s) and that any questions about this information have been answered.

Signature of Physician Obtaining Consent

Date

Printed Name of Physician Obtaining Consent

Assent to Participate in Research (Ages 7 to 11 years old)

Unrelated Donor Reduced Intensity Bone Marrow Transplant for Children with Severe Sickle Cell Disease

You are being invited to be in a research project. This research project is about seeing if transplants can help children who have severe sickle cell disease. People with sickle cell disease do not make healthy red blood cells. In this research project, doctors will see if a bone marrow transplant can help children with sickle cell disease make healthy red blood cells. You should talk to your parents about this research project. If you have questions, ask your parents or your doctor.

Before the transplant, your doctors will give you medicines so that your body will let the new cells grow. These medicines are not as strong as the ones that have been used before and are called reduced intensity medicines. The medicines may make you throw up, lose your hair or have mouth sores.

After the medicines, you will get a transplant of new cells from an unrelated donor. An unrelated donor is a person you do not know. The cells will come from the donor's bone marrow. The cells should make new and healthy red blood cells in your body. Sometimes the donor's cells can cause a problem called GVHD. GVHD can give you diarrhea, a skin rash, or make you not feel hungry. Your doctors will give you medicines to try to make sure that you don't get GVHD. Sometimes the donor cells may not establish themselves and grow in your body. If donor cells are rejected from your body, your own blood cells will grow again and your sickle cell disease problems will come back.

You will stay in the hospital for several days before your transplant and for about four weeks after your transplant. After you go home, you will need to go back to see your doctors often.

You don't have to be in this research project. Your doctors and nurses will not be mad at you if you don't want to be in the research project. If you decide you don't want to be in this research project, you should talk to your doctor and parents about other things to do for your disease.

Sign your name on the line below if you want to be in this research project. You can keep a copy of this form at home.

Minor's Signature

Date

Print Name of Minor

Age of Minor

Certification of Counseling Healthcare Professional: I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been

explained to the above individual and that any questions about this information have been answered.

Counseling Healthcare Professional

Date

Assent to Participate in Research (Ages 12 to 17 years old)

Unrelated Donor Reduced Intensity Bone Marrow Transplant for Children with Severe Sickle Cell Disease

Patients with sickle cell disease have a defect in hemoglobin. Hemoglobin is a protein in red blood cells (RBCs) that carries oxygen to vital organs such as the brain, heart, lungs and kidneys. When hemoglobin is damaged the RBCs are sticky and look like a sickle. The damaged RBCs cannot flow well through blood vessels, and block oxygen and nutrients from reaching organs. This can damage almost all the organs in the body. It is especially bad when vital organs are involved.

Recent studies have shown that a bone marrow transplant from a brother or sister can replace the damaged RBCs with healthy red blood cells. Because of the risks of a bone marrow transplant, transplants are usually only given to patients with severe complications. Usually a bone marrow transplant is only done if the patient has a brother or sister as a donor who has the same ‘tissue’ type. Before a transplant, patients receive high doses of chemotherapy called conditioning to allow donor cells to grow in the patient. Since most patients with severe sickle cell disease do not have a brother or sister with the same tissue type, they do not receive a transplant. These patients often receive medicines and red cell transfusions to try to control symptoms and organ damage. These treatments may be given for many years.

This is a research study of unrelated donor transplantation in patients with severe sickle cell disease. There will be as many as 30 patients with sickle cell disease participating in this research study. It is being done to learn if the intensity of the conditioning can be reduced to reduce the side effects or toxicities and if bone marrow transplants from unrelated donors can help patients with sickle cell disease make healthy red blood cells. In this study, patients who do not have a brother or sister with the same tissue type can receive a transplant from an unrelated donor. The cells for the transplant can come from bone marrow. Bone marrow cells are donated by volunteers who agree to donate some of the cells made in their bone marrow.

You are being invited to join this research study because you have severe sickle cell disease. Because your red blood cells cannot flow well through your blood vessels, this has caused problems with your brain, lungs, or other parts of your body. That is the reason that you have pain, breathing difficulties or weakness. Your doctors think that a transplant may be an option for you.

This form gives you information to help you decide if you want to be in this study. You should read this form and ask any questions you have before agreeing to be in the study. It is up to you to decide if you want to be in the study.

What other choices do I have if I do not take part in the study?

If you decide not to participate in this study, your doctor will discuss other treatment options with you and your parents. Other choices may include:

- Treatment with drugs such as hydroxyurea that can lessen complications of severe sickle cell disease
- Experimental treatments with new drugs for severe sickle cell disease
- A transplant using bone marrow without being part of this study
- Other treatments such as regular RBC transfusions to try to control symptoms related to your severe sickle cell disease

Why is this study being done?

This research study is being done to answer the following questions:

1. Is it safe to do a transplant in patients who have severe sickle cell disease using bone marrow from healthy unrelated donors?
2. Is a “reduced intensity” transplant effective and safe in performing unrelated donor transplants? This “reduced intensity” approach will use a new combination of drugs at reduced doses compared to those previously used for traditional transplants.
3. After the transplant, will the patients with severe sickle cell disease make healthy red blood cells and be protected from health problems of severe sickle cell disease?

What will happen if I take part in this research study?**Before enrolling on study:**

Your doctor will check to see if you have a type matched bone marrow donor available for your transplant.

Before the transplant:

You will have several tests done to check your organ function. These tests will check your heart, lungs, and brain. Most of these tests are X-rays or scans, questions, or blood tests. The doctors will look at the results of all these tests to make sure that it is okay for you to have a transplant.

A central line will be placed in your chest in the operating room (you will be asleep for this). A central line makes it easier for you to receive drugs and for drawing blood for tests (you will not be poked for blood tests or receive shots).

Preparation for the transplant:

Before the transplant, you will need to receive medicines so that your body can accept the new bone marrow cells. This is called a ‘preparative regimen.’ Before the transplant, you will be given 3 drugs. You will get the first drug called alemtuzumab for 4 days about 3 weeks before your transplant. You will go home and return to the hospital to stay 8 days before your transplant. At that time you will get two more drugs called fludarabine and melphalan. All these drugs are given through your central line.

Three days before the transplant, you will also get medicines to suppress your immune system.

These medicines are given to allow the donor cells to grow. There are many drugs that can be used to suppress your immune system. The names of these medicines are tacrolimus, methylprednisolone/prednisone, methotrexate, and cyclosporine.

Bone marrow - infusion of cells:

Bone marrow from an unrelated donor will be used for the transplant. These cells will be given through the central venous catheter, just like a blood transfusion. On the day of your transplant, the new bone marrow cells will be given through your central line.

Post-transplant follow-up and care:

After the transplant you will continue to get medicines to help the donor cells grow. These drugs will also help lower the chance of getting graft versus host disease (GVHD). GVHD is a complication that happens when the donor's cells attack your body. You will receive one or more medicines to prevent GVHD. You will continue to receive these drugs for at least 6 months after the transplant.

You will be in the hospital for about four weeks after your transplant. You will be allowed to go home from the hospital when your doctor feels it is safe. After you go home you will need to return to visit your doctors so they can check your recovery. Your doctors will need to check your blood and bone marrow after the transplant to make sure the new blood cells are growing in your body. Your doctors will also do blood tests and other tests to make sure your organs are working well. When blood is needed for these tests it will be drawn through the central line.

Can the doctor who is the Principal Investigator withdraw me from this study?

You can be taken off the study (with or without your consent) for any of the following reasons:

- You need a medical treatment not allowed in this study
- The investigator decides that continuing in the study would be harmful to you
- You become pregnant and the study participation could be harmful to the fetus
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH)

What are the risks of being in this study?

The drugs may cause a skin rash, hair loss, nausea and vomiting, diarrhea and infections. Your blood counts will fall and you may get fevers, infections or start bleeding. You may also get mouth sores. These are temporary and you will feel better as your new bone marrow grows.

Since you will not be able to fight infections while your new bone marrow is growing back, you may need to get antibiotics. You may also need to get blood transfusions since your new bone marrow will not be making new blood cells right away.

Even with medicines to prevent it, you may get GVHD. This can cause skin rash, vomiting, diarrhea, stomach pain, lung and liver problems, swelling of the hands and feet, dry eyes, stiff joints, and tiredness. These problems are usually mild but can become very serious and prolonged. Medicines are given to prevent GVHD during and after transplant. If GVHD occurs even after taking these medicines, other medicines will need to be started and hospital stays may

be necessary. The medicines used to treat GVHD also have side effects. They can cause tiredness, depression, sleep problems and mood swings. They can also make you get severe infections very easily. Your doctors will do their best to make you feel better and keep you safe. Often this may require many hospital stays. However, it is important to understand that there is a small risk (about a 1 in 10 chance) that you may die as a result of one or more of the complications of unrelated donor transplantation.

It is possible that instead of new bone marrow, your old red blood cells will grow back. If it does, you will continue to have severe sickle cell disease and its problems.

Are there benefits to taking part in the study?

You may or may not benefit from taking part in this study. If the transplant is successful, you may benefit by not having further symptoms and complications of severe sickle cell disease. The knowledge gained from this study may help other patients with severe sickle cell disease.

What are your rights if you decide to take part in this study?

It is up to you if you want to participate in this research study. If you leave the study you can still get medical care from your doctor and transplant center. You will be told about new information or changes in the study that may affect your health or your willingness to continue in the study.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

You will receive a copy of this form. If you need more information about this study, ask the study doctor.

Minor's Assent

I have read the information in this consent form and have had the study explained to me. My questions have been answered to my satisfaction. I agree to participate in the study.

Signature of Minor_____
Date_____
*Print Name of Minor*_____
*Age of Minor***Certification of Counseling Healthcare Professional**

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this information have been answered.

Counseling Healthcare Professional_____
Date