Informed Consent form for Transplant and Additional Follow Up as Part of a Research Study

[Insert site logo and/or address]

TITLE: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Principal Investigator: [Insert site PI]
Co-Investigators: [Insert site co-I]

Study Coordinators: [Insert site study coordinator/s]

[Insert site department/facility name, address, and phone number]

Source of Support: National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (the NIH), Bethesda, Maryland

CONSENT FOR AN ADULT TO BE A SUBJECT IN CLINICAL RESEARCH AND AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES.

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. This research study will include only people who choose to take part. Please take your time to make your decision about taking part in the study. You may discuss your decision with family and friends. You should also discuss this with your healthcare team. If you have any questions, you can ask the Study doctor for more explanation.

1. Introduction

You previously agreed to be part of a research study at [Insert institution]. The people who take part in research studies are called "participants". This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. You are being asked to sign this consent form because you have been assigned to the "donor arm" of the clinical trial. Before you decide if you would like to participate on the "donor arm" of the study, we want you to know why we are doing this study. Being in this study is voluntary. You do not have to take part in this study. If you decide not to participate on the "donor arm" we will continue follow you for two years unless you tell your doctor you do not want to be followed. Do not join this study unless all of your questions are answered.

After reading and discussing the important information in this consent form you should know:

- Why this research study is being done
- What will happen during the study
- Any possible benefits to you
- The possible risks to you
- How your personal health information will be treated during the study and after the study is over
- Whether being in this study could involve any costs to you
- What to do if you have problems or questions about this study

Please read, or have read to you, this consent form carefully. After you finish, talk with the study doctor and ask questions. You may also want to talk to family, friends, your primary care doctor or other health care provider about joining this study. If you decide that you would like proceed with HCT/BMT, you will be asked to sign this form. You will be given a copy of the signed form to keep.

Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to read and discuss with family or friends before making your decision. There are also names and telephone numbers of people you can call to get answers to any questions you may have now or at any time during or after the study. You may change your mind about staying in the study at any time. However, due to the nature of the treatment provided during this study, it might not be safe for you to immediately stop being in the study. If you have any questions about your staying in the study, please talk with the study doctor or study team.

This research study is sponsored by National Heart, Lung, and Blood Institute of the National Institutes of Health (the "Sponsor"). [Insert institution] is being paid by the Sponsor to conduct this study.

If you choose to take part in this study, it is important that you give a true and complete medical history. You must be honest about your past and present use of medications. Information that is untrue or incomplete could have very serious effects on your health and safety during the study.

2. Background

Your doctor has already explained your Sickle Cell Disease (SCD) and how a hematopoietic cell transplant (HCT/BMT) (also referred to as a bone marrow transplant or BMT) can be used to treat your SCD when you first joined the study. The HCT/BMT replaces the defective Sickle blood cells with blood cells from a healthy donor who could be a sibling or an unrelated donor with a tissue-type match that is similar to yours. HCT/BMT may stop the disease and its health problems. HCT/BMT for SCD is successful in children but has not yet been tested in very many adults.

In this study, we assign patients to two treatment options: HCT/BMT or standard of care (this is the same treatment you now receive for your SCD). The treatment is assigned based on whether you have a tissue-type matched (also known as HLA-matched) donor; if you have a donor, you are assigned to the donor treatment arm and will be offered HCT/BMT. If you do not have a donor, you are assigned to the no donor treatment arm and will continue with on-going care. By comparing the health outcomes for patients who receive HCT/BMT to those patients who receive standard of care (regular/routine care), we will be able to determine whether the two treatments are the same, or if one is better than the other.

The study will recruit 200 subjects with severe SCD from approximately 40 hospitals in the United States. Approximately a third of subjects (60 subjects) will be assigned to the donor arm and are eligible for transplant (HCT/BMT). The remaining 140 subjects will be assigned to the 'no donor arm' and will continue to receive ongoing standard of care treatment for SCD.

We found a tissue-type matched donor for you. Therefore, you are assigned to the donor treatment arm and will undergo a bone marrow transplant if you sign this consent form.

Your doctor already determined you were eligible for this study, but to be eligible for transplant:

- Your liver must be healthy enough for transplant
- Your brain MRI must show that you have not had a recent neurologic event (such as stroke) within 30 days of starting transplant conditioning. If you did have a neurologic event, your transplant will be put on hold for 6 months. After the 6 months, the brain MRI will be repeated to see if your brain has healed.
- You must not have HLA (tissue-specific) antibodies against your donor
- You must be willing to use approved contraception until you have stopped taking all the medicines that work against your immune system
- Your donor must be healthy enough to donate and willing to donate bone marrow.

3. Purpose

The purpose of this research study is to:

- To compare outcomes in patients with SCD who undergo HCT/BMT with those who do not undergo HCT/BMT because of the lack of a donor.
- To learn if it is possible and safe to treat persons with severe SCD by HCT/BMT from related and unrelated donors using a pre-transplant preparation with the chemotherapy

drugs busulfan, fludarabine and anti-thymocyte globulin and to document serious side effects due to HCT/BMT (both expected and unexpected).

For 2 years from enrollment, you will undergo study-related tests and results will be made available to study team. Between years 3 and 10 from enrollment, we will ask your doctor annually whether you are alive or dead and the date of last contact with your doctor. If you are not alive, we will ask for the date of death and the cause of death. If you doctor has lost contact with you, we will search the National Death Index, maintained by the government to record all deaths that occur in the U.S. Through the National Death Index, we will obtain the date of death and the cause of death.

4. Study Treatments and Tests

We found a tissue-type matched donor for you, so you have been assigned to the donor arm. You have already signed a consent which told you about the study procedures and follow up. This consent form will go over transplant and additional donor-arm specific follow up.

Before your transplant:

- Before your transplant, the BMT doctor will need to determine if you are healthy enough for transplant. These transplant-related screening assessments include:
    - If you are a female who can bear children, a blood pregnancy test (about 1 teaspoon of blood will be drawn for this purpose)
    - MRA/MRI of the brain (tests that show a detailed view of the brain and its blood vessels)
    - MRI of your liver may be required if you meet certain criteria based on this history of your SCD.
        - A liver biopsy may be required based on the results of your [liver] MRI.
- If you are determined to be healthy enough, you will proceed to transplant. If you are not healthy enough, you will not have a transplant and will continue receive standard of care from your SCD doctor.

Preparation for your transplant and transplant conditioning:

- Transplant Conditioning is the chemotherapy and other medicines given to prepare you to receive donor bone marrow cells. It will help stop your immune system from attacking the donor cells and blocking engraftment or the donor cells 'taking'. You will receive these medications before the bone marrow transplant. These medications will be given in the hospital.
- If you are taking hydroxyurea, this medication will be discontinued at least one week before you start the conditioning therapy.
- To help with providing medicines, blood transfusions and obtaining blood for lab tests, a central venous catheter will be used. This is a hollow tube that is placed by a surgeon or radiologist, usually in the operating room. 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 arms. Once the catheter is placed, it will need daily care at home with cleaning and injection of medicines to prevent catheter-related blood clots. The doctor doing the procedure and the anesthesiologist will describe the risks of

the procedure before the surgery. You or your family members will be instructed on the care of this catheter.

- Transplant Conditioning Regimen:
  - The first medication you will be given for conditioning is called **fludarabine**, which will be given intravenously or IV (using the central venous catheter) for a total of 5 days prior to the transplant.
  - The second medication is called **busulfan**. This drug will also be given IV through the central catheter for 4 days prior to the transplant.
  - The third medication is called **anti-thymocyte globulin (ATG)**, and will also be given IV. The ATG will also be given for 5 days before the transplant.
- Each of these drugs used in this bone marrow transplantation is routinely used as part of a conditioning regimen before transplant and to prevent graft versus host disease. The Food and Drug Administration (FDA) Approval Status of each drug is listed below.
  - Busulfan: FDA approved in adults in the conditioning regimen for bone marrow transplant, but not an FDA labeled indication in children.
  - Fludarabine: FDA approved as treatment for follicular lymphoma. Use in bone marrow transplantation is not an FDA labeled indication.
  - Anti-thymocyte globulin is approved in adults in the conditioning regimen for bone marrow transplantation but this is not a FDA labeled indication in children.

Transplant and Post-Transplant Care:

- On the day of transplantation, you will receive the bone marrow infusion that will be given through the central venous catheter. Your blood pressure, heart rate, respiration rate, and temperature, will be taken before and during the infusion. The study doctor may also give you medications before the marrow infusion to prevent side effects or discomfort.
- After bone marrow transplantation, you will receive additional medications to help prevent a condition called graft-versus-host disease (GVHD). GVHD will be explained more later on in this document.
  - The first medication is called **methotrexate.** Methotrexate will be given on Days 1, 3, 6, and 11 following the bone marrow transplantation.
  - The second medication that you will receive is a class of medicines called a **calcineurin inhibitor (Cyclosporine A or Tacrolimus)**. The calcineurin inhibitor will be given IV starting on Day 3 before the bone marrow transplantation and will be given until Day 180. After Day 180, a tapering of this medicine (gradual decreasing of the amount given) will start and will continue until it has been stopped. The dose may be modified by the study doctor if there is evidence of GVHD or if there is worry about the possibility of a graft rejection.

Additional Donor Arm Follow-Up:

- We will study the side effects of transplant (BMT) including those that are expected and unexpected in addition to the assessments described in the consent form you already assigned. These additional follow up assessments include:
  - Weekly physicals and GVHD assessments from day 7 to day 100 post-transplant.
  - White blood cell chimerism assessment at day 28, day 100, 1 year, and 2 years.

- Red blood cell chimerism assessment for research at day 100 and 2 years
- MRA/MRI of the brain (tests that show a detailed view of the brain and its blood vessels) at 2 years

5. Risks and Discomforts

You may experience discomfort, injury, and other risks as a result of taking part in this study, some of which are not currently known at this time. You may also learn medical information about you that you were previously unaware of and would rather not know. Also, your condition may not get better or may get worse during this study.

By taking part in this research study, you are at risk to a number of complications, some of which can be severe and sometimes fatal. The most serious and commonly encountered include:

Graft-versus-Host Disease (GVHD):

This condition results from white cells called T cells in the donor's bone marrow cells recognizing your body as foreign and attacking it. You are more likely to get GVHD if the donor's tissue type does not match your 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 a 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. Some patients who have GVHD have developed collections of fluid around the heart (known as a pericardial effusion) or other body spaces such as around the lungs. These fluid collections may interfere with heart or lung function and may require surgical drainage or other treatments. To confirm the diagnosis of acute or chronic GVHD, you 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 at least a 10-20% chance that you will develop GVHD after the transplant. The risk of GVHD is higher after an unrelated donor transplant. You 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. Chronic GVHD can also occur 3 or more months after transplantation and may be associated with a prolonged course. GVHD can range from mild to life-threatening. 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. It is possible that GVHD can leave you with chronic medical problems which are worse than symptoms or disability you currently experience due to sickle cell disease. Sometimes GVHD is severe or difficult to treat and may lead to death.

Susceptibility to bacterial and viral infections in the early post-transplant period:

In the early post-transplant period, you will have an increased chance of getting bacterial or viral infections. This is because your ability to fight infections will be greatly limited due to the drugs given to prepare you for the bone marrow transplant.

Potential risk of reversible brain injury RPLS/PRES and bleeding in the brain:

Patients with sickle cell disease who have a bone marrow transplantation 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) a form of injury to the brain, which is usually reversible. 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. It is likely that about a quarter of the patients are at risk to develop RPLS/PRES. All sickle cell patients who develop RPLS/PRES typically can be successfully treated for this complication. We do not anticipate RPLS/PRES in any patient more than 6 months from their date of transplant. We believe that patients 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.

A very small number of patients with sickle cell disease have experienced bleeding in the brain after a bone marrow transplant. While this complication is rare, it is very serious because it can cause permanent brain damage or death. Your doctors will keep your platelet count in a safe range and monitor you carefully to keep you safe and prevent bleeding in the brain.

If you experience any of these side effects or changes in mental status, you should contact your 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.

Potential risk of drugs used to ensure engraftment of new bone marrow cells:

To reduce the risk that the new bone marrow will not "take" or grow, you will receive the medications listed previously, **fludarabine, busulfan**, **anti-thymocyte globulin** before transplantation. These drugs have possible side effects which include:

Fludarabine: Can cause rare side effects such as: temporary blindness, confusion, and coma. Infrequent side effects such as poor kidney function, common side effects such as mouth sores and likely side effects such as nausea, vomiting, and diarrhea.

Fludarabine

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
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	Pneumonia Diarrhea Mouth sores Skin rash Fever Swelling of hands and feet	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

Busulfan: Can cause rare side effects such as: infertility (inability to have children) and lung injury when used at high doses or for prolonged periods of time. Infrequent side effects such as seizures, common side effects such as sores in the mouth and darkening of the skin, and likely side effects include nausea, vomiting, and hair loss.

Busulfan

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
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	Diarrhea Inflammation of the lung Weakness Weight loss	Low blood pressure Excessive perspiration Allergic reaction Damage/ scarring of lung tissue Sterility Seizure

Anti-Thymocyte Globulin: Is an antibody (made in rabbits) which can cause rare side effects such as seizures and increased risk of infection, infrequent side effects such as joint pain or allergic reaction (with low blood pressure, fast heart and breathing rate, difficulty breathing, and hives) and anemia, and common side effects such as fever and rash.

Anti-Thymocyte Globulin

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
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	Nausea Vomiting Diarrhea Rash Headache Sweating Back pain Severe itching Allergic reaction of skin and blood vessels Tiredness Loss of appetite	Abdominal pain Dizziness High blood pressure Blisters Pain in the muscles Herpes simplex infection Inflammation of the throat

Potential Side Effects of Drugs used to prevent GVHD

Although we have learned much about how to prevent the disease, graft-versus-host disease may be difficult to treat once it occurs and the complications associated with it can be life-threatening. The treatments that have been used to prevent graft-versus-host disease include the use of drugs, like **Cyclosporine A** and **Tacrolimus**, to suppress the activation of lymphocytes.

Calcineurin inhibitor (Cyclosporine or Tacrolimus): Can cause rare side effects such as temporary blindness, seizures, confusion and coma, common side effects such as poor kidney function and in some cases a need for dialysis (rare), increased risk of infection, swelling of the gums, infrequent side effects include numbness/tingling/tremors in hands and feet, and some likely side effects include high blood pressure, increased body hair, and chemical imbalances.

Cyclosporine: This drug may be used for all patients.

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
High blood pressure Kidney problems Headaches Nausea Vomiting Stomach pain or indigestion Swelling of the hands or feet	Tremors Increased hair growth	Muscle cramps Numbness and tingling of the hands or feet Seizure

Tacrolimus: This drug may be used for all patients.

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
Anemia Loss of appetite Diarrhea High potassium levels High blood pressure Nausea Fever Headache High blood sugar	Hair loss Vomiting Tingling sensation in the extremities Itching Rash Abdominal pain	Confusion Painful joints Increased sensitivity to light Blurred vision Insomnia Infection Jaundice Kidney injury Seizures

Methotrexate: Can cause depression of the white blood count early after transplant, transient alteration in liver function and can result in severe mouth sores.

Methotrexate

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
High levels of liver enzymes	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	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

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 and sometimes as a complication of GVHD. 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, you 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 immune system may take many months following the initial recovery of your cell counts. During this time, there is an increased risk of infections. You will be prescribed certain medications to reduce the chance of those infections. However,

preventive treatments are not always effective. If you have an infection, you 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.
There is a risk that the new marrow will fail to "take" and grow after transplantation. This is called graft rejection. If this happens, your own marrow will recover meaning that symptoms of your sickle cell disease such as pain crises and other complications will return. Your blood will be evaluated frequently after transplantation to determine if the new donor bone marrow is recovering. In the event that your marrow does not recover as expected, stimulating the bone marrow cells by drugs, performing second bone marrow transplantation or giving bone marrow from another donor are treatment options. If you develop graft rejection, you will stop being in this study but you will continue to receive the standard medical care. Delay or failure of bone marrow recovery increases the risk period of infection and the need for blood transfusions.

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.

Pregnancy:
For Women:
The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated in this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods of contraception to avoid pregnancy while you are being treated in this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated in this study. Since treatments may alter/disrupt normal menstrual cycles, resulting in missed or absent periods, natural methods of family planning should not be used. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your doctor immediately.

If you are nursing a baby, the medications used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the treatment, so talk to your doctor about the length of time you need to avoid nursing.

For Men:
The treatment on this study can damage testicular function. You should not father a child while in this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use an effective method of contraception to avoid pregnancy or you must not have sex. The study doctor will talk to you

about the acceptable methods to avoid pregnancy while you are being treated in this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated in this study. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your doctor immediately.

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. However, it is difficult to know the exact risk of sterility after transplant with the use of this conditioning regimen. Since there is a high risk of infertility after a bone marrow transplant in both males and females we will refer you to a fertility preservation center to discuss your options. These may include storage of sperm/eggs or tissue from ovary or testes.

Risk of death
Some of the side effects of an unrelated donor transplant may be very severe and may cause death despite using all supportive care. Though all precautions will be taken to make the transplant as safe as possible for you, there is still a 10% - 20% chance of death following unrelated donor transplantation.

Oher Risks
As with any procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life-threatening. You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. Possible Benefits

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

7. Other Treatments

You do not have to participate in this study. Your participation is ***voluntary***. If you choose not to participate in the study, you will not be missing out on any standard therapy for sickle cell disease. You will receive the same excellent care from the doctors and nurses whether or not you decide to take part in this study. In addition, other types of transplants are currently available to

you. In some cases, the source of the stem cells is different from bone marrow. You may also choose to receive a transplant that uses a different combination of medications or a higher or lower dosage of the same medications. The different transplant treatment plans each will have different risks and benefits. Your doctors can discuss each type of transplant with you in greater detail.

8. Costs and Reimbursements

Several of the tests and treatments given in this study are considered standard care and will be billed to you or your insurer in the usual way. This study is also approved by Centers for Medicare and Medicaid Services (CMS) for reimbursement. Standard costs include those of your 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.

The study will pay for the research-related items or services that are provided only because you are in the study as outlined above. If you get a bill you think is wrong, call the researchers.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed for your care
- Monitoring for side effects or other problems
- Treatment of complications
- Deductibles or co-pays for these items or services.

If you do not have a health plan or if you think your health plan may not cover these costs during the study, please talk to the researchers or call your health plan's medical reviewer. It is recommended that you work with your health care team to find out about costs in advance.

If you receive a bill, or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or [Insert institution] Patient Billing Services.

You and/or your health insurance will be charged, in the standard manner, for services and procedures provided for your routine care. Any deductibles, co-insurances or co-payments that are a part of your insurance coverage will apply.

9. Compensation of Payment

You will not receive additional compensation for participating on the transplant portion of this clinical trial. You will continue to receive compensation for the health related questionnaire and the electronic pain diary as was explained to you when you previously agreed to participate on this trial.

10. Physical Injury as a Result of Participation

[Insert institution] researchers and their associates who provide services at the [Insert institution] recognize the importance of your voluntary participation in their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

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 insurance company. If you think that you have suffered a research-related injury, let the study doctors know right away. It is important that you tell your doctor, [Insert Investigator], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at [Insert telephone]. You will receive medical treatment if injured as a result of taking part in this study. Your insurance will be charged for this treatment. The study sponsor, the National Heart, Lung, and Blood Institute, does not offer financial compensation or payment if you are injured as a result in participating in this research study. However, you are not giving up any legal rights by signing this form.

It is possible that [Insert institution] may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below.

11. Rights as a Participant

Your participation in this research study, including the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for your participation in this research study will have no effect on your current or future relationship with the [Insert institution]. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a [Insert institution] hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your physician is involved as an investigator in this research study. As both your physician and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

You may choose to either take part or to not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision is made, there will be no penalty and you will not lose any of your regular benefits. If you leave the study, you can still get medical care from your doctor and transplant center. We will tell you about new

information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any legal rights to seek payment by signing this form.

If you have questions about your rights as a research participant or if you have questions, concerns or complaints about the research, you may contact the [Insert institution] Institutional Review Board (IRB) at the toll-free number [Insert IRB Number].

12. Ending Your Participation

You may withdraw your consent, at any time, for your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for your participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

If you are thinking about withdrawing from this study, talk with one of the research team members and your regular doctor first so they can help you decide what may be best for your medical care once you are off study. **However, withdrawal after initiation of treatment could be life-threatening or even fatal, and may not be reasonable.**

If you leave the study before the planned final visit, the study doctor may ask to have some of the end of study procedures done for your safety and well-being.

Your study doctor or NHLBI may decide to take you out of the study if:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in this study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

13. Privacy, Confidentiality, and Use of Information

By signing this consent form, you are giving the researchers your permission to obtain, use, and share information about you for this study, and are required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Information from your hospital or office health records that may be reasonably related to the conduct and oversight of the research study. This may include information about hospital admissions or visits during this study, so that we know about any possible problems or side effects. If health information is needed from your doctors or hospitals from other institutions, you will be asked to give permission for these records to be sent to the researchers.
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

Any information about you obtained from this research will be kept as confidential (private) as possible. Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations protect your privacy, restrict who is allowed to look at your records, and require security to protect your records. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a unique study ID number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

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.

Information gathered during this study and your medical records may be inspected and verified by staff of the study sponsor (the National Heart, Lung, and Blood Institute/National Institutes of Health), Office for Human Research Protections, [Insert institution], or the Institutional Review Board (IRB). Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records shared outside of [Insert institution]. For records shared outside of [Insert institution], you will be given a study ID number. The list that can match you to the study ID number will be kept in a locked file cabinet in [Insert location].

Organizations that may look at and/or copy your 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

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the sponsor of this research study, the National Institutes of Health, or the Office for Human Research Protections or the Blood and Marrow Transplant Clinical Trials Network will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the [Insert institution] cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical information related to your participation in the study.

Authorized representatives of the [Insert institution] or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of: (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

At the end of the study, the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI) will be given data from the study, without personal identifying information such as your name, address, Social Security number, or Medicare number. The data and/or materials may be shared with other scientists who meet NHLBI requirements, including treating the data or materials as medically confidential, obtaining approval from their Human Subjects review boards, and agreeing not to share the data or materials with other parties.

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of seven years after final reporting or publication of a project. The study results will stay in your research record at (*insert Institution*) for ten years from enrollment. Beyond the funding period (5-years), the dataset will be transferred to the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin for extended follow up. Research information in your medical record will be kept indefinitely. Data regarding your clinical situation, including follow-up after 2 years, may be obtained from the CIBMTR, which captures information on all US transplants.

In accordance with the [Insert institution] Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

14. Health Insurance Portability and Accountability Act (HIPAA)

HIPAA 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 individual health information for the purpose of conducting the research study entitled *Bone Marrow Transplantation for Adolescents and Young Adults with Severe Sickle Cell.*

b. Individual Health Information to be Used or Disclosed: My 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 Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from: *(list: hospitals, clinics or providers from which health care information can be requested)*

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_____

_____

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me 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 #1503 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

The Blood Center of Wisconsin (BCW), which is a central lab that will do specialized testing on blood samples required during the study

Data Warehouse Consultants (DWC) which is an agent of Emory University that will manage the pain diary. DWC will have access to your phone number, email address, IP Address and data that is entered in the pain diary application.

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

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I 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 me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My 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.

15. For More Information

If you'd like more information about this study, or if you have any problems while you're participating in this study, you can contact the study doctor or staff. They may be contacted at the telephone numbers listed here:

[Insert name and contact details]

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 you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, [Insert institution and number] to discuss problems, concerns, and answer any questions I have about my rights as a research participant, to obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

______________________	______________________	__________
Signature of Participant	Participant's Printed Name	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

______________________________	______________________
Printed Name of Person Obtaining Consent	Role in Research Study
______________________________	______________________
Signature of Person Obtaining Consent	Date

Assent to Participate in Transplant and Additional Follow Up as Part of a Research Study

[Insert site logo and/or address]

TITLE: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Principal Investigator: [Insert site PI]
Co-Investigators: [Insert site co-I]

Study Coordinators: [Insert site study coordinator/s]

[Insert site department/facility name, address, and phone number]

Source of Support: National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (the NIH), Bethesda, Maryland

CONSENT FOR A MINOR TO BE A SUBJECT IN CLINICAL RESEARCH AND AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES.

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. This research study will include only people who choose to take part in the study. Please take your time to make your decision about taking part in the study. You may discuss your decision with family and friends. You should also discuss this with your healthcare team. If you have any questions, you can ask the Study doctor for more explanation.

A. Why am I here?

We are inviting you to join our study because you have severe sickle cell disease. You are now receiving blood transfusions, hydroxyurea, and/or pain medicines. There is another treatment called bone marrow transplant. A transplant uses blood-making cells from another person (donor) to replace your cells that are not healthy (the sickle red blood cell). A donor is the name for a person who gives some of their blood-making cells for a transplant and their tissue has to match your tissue. We have identified a donor for you and inviting you participate in this study to receive the treatment called bone marrow transplant.

B. Why are you doing this study?

We know transplant works to cure your disease, but we don't know if this is a better treatment than blood transfusions, hydroxyurea, and/or pain medicines.

C. What will happen to me?

Before your transplant, you will get a small tube put in your chest in the operating room (you will be asleep for this). The small tube makes it easier for you to get your medicines. It will also make it easier for drawing blood for tests because you will not be poked.

We will give you medicines that will help make the cells from your donor grow in your body. These medicines might make you feel sick. You might throw up, lose your hair, or get sores in your mouth.

After you're done taking the medicines, you will get cells from your donor. This is your transplant. Your new cells will come from your donor's bone marrow. The cells will make new and healthy cells in your body.

Sometimes the donor cells can cause a problem called graft versus host disease (GVHD). GVHD happens when the donor cells attack your body. It can give you diarrhea, a skin rash, make you feel sick and throw up, or make you not feel hungry. Your doctors will give you medicines to try to make sure you don't get GVHD.

You will stay in the hospital for several days before your transplant and for about 4 weeks after your transplant. After you go home, you will need to go back to see your doctor often.

It is possible that your disease will come back. If this happens, your doctor will find another way to treat you.

D. Will it hurt?

For your transplant, we will put a small tube in your chest. It might hurt a little and you might bleed a little. Your doctor and nurses will make sure you feel as little pain as possible.

E. Will the study help me?

We know bone marrow transplant can cure sickle cell disease. What we don't know is whether some of the problems from transplant like GVHD can cause more harm that if you did not have a transplant and continued to receive the care you are receiving now.

F. What if I have questions?

You can ask any questions that you have about the study. If you forget to ask a question and think of it later, you can call me [*insert office number*]. You can also ask your question the next time you see me.

You can call the study office at any time to ask questions about the study.

G. Do I have to be in this study?

You don't have to be in this study. Your doctor and nurses will not be mad at you if you don't want to join. If you decide you don't want to be in this study, you should talk to your doctor, nurses, and parents. You will receive the care you are receiving now (pain medication, blood transfusion, or hydroxyurea).

You can say yes now and change your mind later.

Be sure to talk this over with your parents before you decide if you want be in the study. We will also ask your parents to give their permission for you to join this study.

Writing your name on this page means that you agree to be in the study and know what will happen to you. If you decide to quit the study, all you have to do is tell your doctor.

You and your parent or guardian will get a copy of this form after you sign it.

_____	_____
Printed Name of Child	Date
_____	_____
Signature of Child	Age of Child

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.

_____	_____
Printed Name of Person Obtaining Assent	Role in Research Study
_____	_____
Signature of Person Obtaining Assent	Date