Informed Consent to Participate in Research

MULTI-CENTER, OPEN LABEL, RANDOMIZED TRIAL COMPARING SINGLE VERSUS DOUBLE UMBILICAL CORD BLOOD TRANSPLANTATION IN PEDIATRIC PATIENTS WITH HIGH RISK LEUKEMIA AND MYELODYSPLASIA

This is a clinical trial, which is a research study to answer specific medical questions. The information from this study will help future patients. The Study doctor (the person in charge of the research) will explain the clinical trial to you and your child. Clinical trials 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 can 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.

Your child is being asked to take part in this study by your child's doctor because your child has leukemia or myelodysplastic syndrome (MDS) that has failed other treatment or your child's leukemia or MDS is not likely to respond to other treatment. These diseases can be treated and sometimes cured with very high doses of chemotherapy and radiation therapy given to kill leukemia or MDS cells. However, this treatment also harms normal cells in the bone marrow. The bone marrow is the body's "blood factory." It makes the cells that circulate in the blood, including: red blood cells (which carry oxygen), white blood cells (which fight infection), and platelets (which prevent bleeding). The bone marrow can be fixed by giving "hematopoietic or blood stem cells" donated by someone else. This is called a hematopoietic stem cell transplant. Blood stem cells are the "parent cells" of the bone marrow that produce all blood cells. For a transplant to be successful, the donor blood stem cells must have a tissue type that is completely or closely matched to the patient's tissue type. Genetic markers on the surface of cells make up our tissue type. These genetic markers are like a "finger print" and help our immune system to determine which cells belong to the body and which do not. For patients needing a transplant who do not have a family donor who is a match (has the same tissue type), blood stem cells from unrelated donors can be used.

Blood stem cells are found in bone marrow and in umbilical cord blood. Umbilical cord blood is the blood left over in the placenta (afterbirth) after a baby is born. Usually this blood is thrown out with the placenta. Over the past 15 years, we have learned how to collect and freeze cord blood cells to be used for transplants at a later time. A cord blood unit is the cord blood cells collected and stored from a single placenta. Cord blood units have been used for more than 6,500 transplants performed around the world. **The purpose of this study is to determine whether giving two units of cord blood to a patient is better than giving one cord blood unit.**

Before you decide whether or not to have your child join the study, please read the information below. Feel free to ask questions to understand your child's rights and protections. It is your choice and that of your child to take part in this study.

Sponsor and source of funding:
This study is sponsored by the National Institutes of Health (NIH), which gives financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The NIH is a government funded research program and the BMT CTN is a not-for-profit group of transplant programs conducting research on hematopoietic stem cell transplant to benefit future patients.

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

- You or your child's insurance company will pay for all medical bills for your child's treatment
- You or your child will not incur additional cost for any research lab tests that are part of this study (i.e., lab tests that are not part of routine care)
- You or your child will not be paid to participate in this study
- Your child will face the same risks and benefits as any other transplant patient

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

What other choices does my child have if my child does not take part in the study?
Your child's other choices may include:

- Treatment with other drugs
- Experimental treatment with drugs or cells
- A transplant with umbilical cord blood that is not part of this study
- A bone marrow transplant from a tissue-type mismatched related donor or from a tissue-type matched or mismatched adult unrelated donor
- No therapy to try to control your child's leukemia but treatment to make sure your child remains comfortable for the remainder of his or her life

Please talk to your child's doctor about your child's treatment choices before you decide to allow your child to take part in this study.

Why is this study being done?
More than 6,500 umbilical cord blood transplants have been done worldwide, mostly in children with leukemia. One important factor affecting the success of a cord blood transplant is the number of cells in the cord blood unit given divided by the recipient's weight (cell dose). Patients who receive a high cell dose ($> 2.5 \times 10^7$ cells/kilogram) have better marrow recovery and a higher rate of survival than those who receive a lower cell dose.

In an attempt to make umbilical cord blood transplantation possible for bigger children, adolescents and adults, researchers have tried giving two cord blood units on the same day for their transplant, one after the other. The data from more than 150 "double cord blood" transplants in adults suggest that the "double cord blood" transplants may allow bone marrow

recovery and survival in patients who do not have a single cord blood unit with enough cells for successful transplantation. It is not known whether giving two units will improve bone marrow recovery or survival over a single unit with a high number of cells.

What the doctors need to know from this study:
Your child's doctor and others would like to know whether giving two umbilical cord blood units will result in faster bone marrow recovery and improved survival compared to giving only one unit of umbilical cord blood that has an acceptable cell dose for your child.

How many children will take part in the study?
Two hundred and twenty (220) patients will take part in this study. Half (110) will receive two umbilical cord blood units and the other half (110) will receive a single umbilical cord blood unit. To be part of the study your child must:

- Be between 1-21 years old
- Have leukemia or MDS
- Have two suitable umbilical cord blood units available
- Have your informed consent
- Give assent if your child is old enough to understand the risks and benefits and sign an assent document

What will happen if your child takes part in this research study? Before enrolling on study:
Your child will have the following examinations, tests or procedures to determine whether your child can be included in the study. These examinations, tests or procedures are required as part of regular pre-transplant care and may be done even if you decide not to allow your child to participate in this study:

- Medical history
- Physical examination
- Blood and bone marrow tests including a bone marrow biopsy to evaluate your child's leukemia
- Other tests such as a spinal tap to evaluate your child's leukemia
- Blood tests to determine whether your child has had prior illness such as HIV, hepatitis and other viral illness
- Heart function tests
- Lung function tests
- Kidney function tests
- If your child is a teenager and female, a blood pregnancy test will be performed to make sure that your child is not pregnant. If your child is pregnant, your child will not be able to take part in this study. The study treatment could be harmful to the fetus.

Randomization:
If your child is enrolled on this study, your child will be randomized to receive either one or two umbilical cord blood units. Randomization means that your child is assigned to a group by chance. This is done using a special computer program. Your child has a 50/50 chance of being in either group. Neither you nor your doctor can choose the group. If your child is assigned to

receive a single cord blood unit, that unit will contain enough cells for bone marrow recovery and survival.

Pre-transplant:
If your child does not have a central intravenous (Hickman) line, your child's doctor will ensure that your child has a central intravenous line prior to transplant. All drugs that may be required during your transplant will be given through the central intravenous line. Blood required for any tests will also be collected from the central intravenous line in an effort to minimize pain. Starting 10 days prior to transplant your child will receive chemotherapy and total body irradiation (TBI). This is called the preparative regimen because it prepares the body to receive the donor (cord blood) cells. The preparative regimen kills leukemia/MDS cells. It also kills cells in the body that would reject the donor cells. The chemotherapy and TBI will also damage your child's normal bone marrow cells. The transplanted cord blood will replace the damaged cells.

The drugs used as chemotherapy are fludarabine and cyclophosphamide (often called by its brand name, Cytoxan). Fludarabine will be given intravenously (through your child's central line) once a day for the first 3 days. Next, TBI will be given twice a day for 4 days. Then cyclophosphamide will be given intravenously (through your child's central line) once a day for 2 days. This will be followed by a "rest day" when your child will not receive chemotherapy or radiation.

Three days before the transplant, and continuing in the weeks after the transplant, your child will receive drugs to allow the umbilical cord blood stem cells to grow up inside your child's body. These drugs decrease the chance of a complication known as graft-versus-host disease (GVHD). GVHD results when the cord blood cells recognize your child's body as foreign and attack it. Your child will receive two standard drugs to prevent GVHD. These drugs are called cyclosporine (also called Gengraf or Neoral) and mycophenolate mofetil (also called MMF or Cellcept).

Transplant day:
On the day of transplant your child will receive either one or two umbilical cord blood units, given intravenously through the central intravenous line. Whether your child receives one or two umbilical cord blood units is decided at the time of randomization. The date of transplant is referred to as Day 0.

Post-transplant follow-up and care:
To speed the recovery of blood cells as much as possible your child will receive granulocyte-colony-stimulating factor (G-CSF or Neupogen). G-CSF is a hormone that tells the bone marrow to make white blood cells. Your child will start receiving growth factor the day after transplant. Your child will continue to receive it daily until his or her white blood cell count recovers.

After your child's transplant, your child will be watched very closely. He or she will have a physical examination and blood tests at least twice weekly. Additional blood tests and bone

marrow tests will be done if your child's doctor thinks it is indicated to take care of your child. Samples of blood (up to 75 ml or 5 tablespoons) and bone marrow (up to 15 ml or 1 tablespoon) will be drawn to evaluate how the new marrow is functioning. The blood tests will be done on Days 28, 42, 60, 100, 180, 1 year, and 2 years after transplantation (Day 0 is the day of transplant and all days are counted from the day of transplant, for example: Day 28 is the 28th day after transplant). If necessary, bone marrow tests will also be done. These examinations and tests are part of regular care after transplant and may be done even if you do not allow your child to join the study and may be done more frequently than described here if necessary for your child's care.

As part of the study your child will have blood samples drawn to evaluate the function of his or her immune system at Day 100, Day 180, 1 and 2 years after transplant. As part of the study, your child will receive tetanus vaccinations at Day 100, 6 months and 12 months. Tetanus re-vaccinations are done routinely after transplantation, since immunity from vaccinations given before the transplant is lost. In this study, your child will be vaccinated earlier than transplant patients are usually vaccinated after their transplant because we want to evaluate how the immune system is functioning and to determine whether vaccination protection can be effective sooner than generally believed. There is no additional risk to receiving this vaccine other than the risk of a tetanus injection.

Your child will be discharged from the hospital when your child's doctor feels he/she is ready. At first, your child will need to visit the bone marrow transplant clinic several times a week for check ups. Eventually, the visits will be less frequent. Your child's doctor will likely want to see your child at 6 months, 1 year, and 2 years after the transplant as part of your child's care after a transplant. In some cases, it may be necessary for your child to visit the transplant clinic more frequently and your child's doctor will determine this. Blood tests other than those mentioned above may also be necessary. Your child's doctor will make this decision.

Follow up for your child's transplant will last as long as your child requires care related to the transplant and afterwards for any of the late complications that may occur from chemotherapy or transplant. We encourage patients who have had a transplant to be followed either by their transplant doctor or another doctor who is familiar with late complications that may arise from transplantation. We would like to keep track of your child's medical condition for the rest of your child's life. We will do this by contacting you (or your child) and the doctor providing your child's regular medical care by phone or mail once a year. Checking on your child's condition every year helps us look at the long-term effects of the study and transplantation in general. Many transplant centers include this type of long-term follow-up as part of their regular medical care. However, it is not necessary for you to agree to follow-up of your child for longer than 2 years in order to participate in this study. If you would like to learn more about long-term care, please discuss it with your child's doctor.

How long will your child be in the study?
Your child will be in the study for 2 years. Your child's doctor (the doctor taking care of your child during his/her transplant or your child's oncologist or your child's primary care doctor), however, will follow your child indefinitely and provide us with information as described above.

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 information requested.

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 tell your child's doctor if you or your child are thinking about stopping so any risks from the medications can be evaluated. Another reason to tell your child's doctor is to discuss what follow-up care and testing could be most helpful for your child.

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 and to continue to allow your child's doctor to tell us about your progress until at least two years post-transplant. You can choose to grant or not to grant this permission.

Can the doctor who is the Principal Investigator withdraw your child (you) 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?
So far, none of the studies using two cord blood units for transplantation show risks that are different from using a single cord blood unit for transplant. However, it is possible that there are new and unknown risks from receiving two cord blood units instead of one. For example, because the double cord transplant gives more donor cells, the frequency or severity of GVHD might be increased. Also, with two cord blood donors, each donor's cells could react against the other, rather than make new healthy bone marrow for the patient. While early studies of double cord blood transplants do not show a risk of either of these problems, we will be monitoring patients carefully during this study to be sure that they do not occur when a larger group of patients are treated.

If your child develops GVHD, your child's doctor will treat the GVHD with the best available treatment. If your child's bone marrow does not grow back as expected, your child's doctor will discuss it with the Principal Investigators of this study and the BMT CTN. We would try to identify another cord blood unit to be used for a second transplant if that is felt to be a good treatment.

Chemotherapy drugs and total body irradiation (TBI) used in this study:
The standard approach for treating patients with leukemia and/or MDS is to give high doses of cyclophosphamide (Cytoxan) and TBI, followed by a transplant using stem cells from donor bone marrow or cord blood. This treatment can cure patients who have these diseases. However, this treatment can also cause short and long-term side effects which can be uncomfortable, and in some cases, dangerous, life threatening, or even fatal (see RISKS AND TOXICITIES RELATED TO STANDARD TRANSPLANT PROCEDURES below). In this study, in addition to TBI and cyclophosphamide, fludarabine is also given in an attempt to improve recovery after cord blood transplants. All patients receiving transplants must also receive GVHD prophylaxis (i.e., drugs to prevent GVHD). The drugs used to prevent GVHD are cyclosporine (CSA) and mycophenolate mofetil (MMF). These drugs are usually well tolerated, but they can cause serious side effects. The most common and most important of these side effects are listed below. Since this combination of treatments is relatively new, there may be additional unexpected side effects.

Everyone taking part in the study will be carefully monitored for side effects. Side effects can be mild or very serious. Your child's doctor and the health care team will give you medications to help lessen the risk of side effects, and make your child more comfortable if they occur. In most cases, the side effects are temporary and reversible. In some cases, side effects may be serious, last a long time or never go away. You should talk to your child's doctor about any side effects that your child has while taking part in this study. A group of experts will carefully watch the side effects experienced by patients on this study. If unexpected, dangerous complications are reported, and the experts determine that these side effects might occur in other patients on the study, you and your doctor will be notified and the study closed. Your child will continue to receive all the care related to his/her transplant.

There are other potential complications that all patients undergoing a transplant face, regardless of whether or not they participate in the study. Be sure to ask your doctor to discuss those with you.

Are there benefits to taking part in the study?
This research study is to determine whether giving two umbilical cord blood units results in faster bone marrow recovery and improved survival compared to giving only one umbilical cord blood unit. At this point doctors do not know whether two umbilical cord blood units are better than one umbilical cord blood unit. The information obtained from this study will help doctors treat future patients with leukemia who require an umbilical cord blood transplant. If one group does better than the other group, and your child is randomly assigned to that group, your child may benefit from being in the study. Beyond that, there are no other specific benefits for your child from taking part in this study.

POTENTIAL SIDE EFFECTS OF STUDY DRUGS

Cyclophosphamide

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.)*
• Decreased white blood cell count with increased risk of infection • Temporary hair loss • Nausea • Vomiting • Loss of appetite • Sores in mouth or on lips • Diarrhea • Stopping of menstrual periods in women • Decreased sperm production in men	• Decreased platelet count (mild) with increased risk of bleeding • Blood in urine • Temporary darkening of nail beds • Acne • Temporary tiredness • Damage to the fetus if your child becomes pregnant while taking cyclophosphamide	• Scarring of lung tissue, with cough and shortness of breath • Severe heart muscle injury and death

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.)*
• Decreased white blood cell count with increased risk of infection • Decreased platelet count with increased risk of bleeding • Tiredness • Nausea • Vomiting	• Pneumonia • Diarrhea	• 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

Cyclosporine

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

G-CSF

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.)*
	• Local irritation (skin) at injection site • Ache or pain inside the bones, increased levels of liver enzymes and uric acid in the blood, low number of platelets in the blood	• 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

Mycophenolate Mofetil

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.)*
• Diarrhea • Stomach pain • Upset stomach • Vomiting • Difficulty falling asleep or staying asleep	• Pain, especially in the back, muscles, or joints • Constipation	• Swelling of the hands, feet, ankles, or lower legs • Difficulty breathing • Shaking hands that you cannot control • Unusual bruising or bleeding • Headache • Fast heartbeat • Excessive tiredness • Dizziness • Pale skin • Weakness • Blood in stools • Bloody vomit • Loose, floppy muscles • White patches in mouth or throat • Swelling of gums • Vision changes • Rash • Low blood counts • Damage to unborn baby • Limited effectiveness of birth control • Progressive Multifocal Leukoencephalopathy

Total body Irradiation (TBI):

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.)*
• Diarrhea • Nausea • Stomach cramps • Vomiting (throwing up) • Painful swelling of the salivary glands under the ears for a few days • Short-term hair loss • Anemia • Infection • Bleeding • Cataracts • Sterility (inability to have children) • Slow growth • Hormone problems (such as thyroid disease or diabetes) • Mouth sores	• Lung inflammation • Pneumonia • Redness of the skin • Serious liver problems	• Risk of developing other cancers in the future • Difficulty swallowing • Back problems • Kidney problems • Learning problems

Most of the problems described above that we anticipate to be common are temporary and treatable.

RISKS AND TOXICITIES RELATED TO STANDARD TRANSPLANT PROCEDURES

Risks of Cord Blood Transplantation
The following problems may occur as a result of the transplantation of umbilical cord blood. These are risks that would be present whether such a transplant was done as part of a study or not:

1. **Slow Recovery of Blood Counts.** The red blood cells, white blood cells and platelets can be slow to recover after umbilical cord blood transplantation. Until your child's blood counts recover, he or she will need blood and platelet transfusions, and will be at

risk for bleeding and infections. Although infections can be treated with drugs, they can be very dangerous or fatal. To speed the recovery of the white cells as much as possible your child will receive growth factor, a hormone that tells the bone marrow to make white blood cells. This drug is very safe but can cause fever, bone pain, feeling tired and, very rarely, allergic reactions.

2. **Graft Failure.** The umbilical cord blood stem cells (the "graft") may fail to grow inside your child's body. Past experience suggests that there can be up to a 20% chance for failure to graft. If graft failure occurs, this will result in low blood counts for a long period of time and can be fatal. Should this happen, your child will not receive additional stem cells from the same cord blood donor. However, your child may be able to receive a second transplant with stem cells from another person (e.g., a different umbilical cord blood donor or an adult donor).

3. **Graft-versus-host Disease (GVHD).** This condition results from the umbilical cord blood cells recognizing your child's body as foreign and attacking it. You are more likely to get GVHD if you receive a mismatched (tissue type) than a matched cord blood unit. In most cases, GVHD can be successfully treated. Sometimes GVHD is severe or difficult to treat and may lead to death. Your child will be watched closely for this complication and given treatment to prevent and treat it.

   There are two forms of GVHD: acute GVHD (occurs in the first 3 months after transplant) and chronic GVHD (after the first 3 months). 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, 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 tissue to look at under the microscope) and possibly a gut biopsy and rarely a liver biopsy.

4. **Genetic Disease within the Cord Blood Cells**. It is possible that certain genetic diseases (for example thalassemia or immunodeficiency) may be passed through the umbilical cord blood stem cells. While these diseases are very rare, each umbilical cord blood can only be tested for a few of the many possible genetic diseases. To reduce this possibility, cord blood is not collected from babies that have genetic diseases running in their family.

5. **Incorrect Labeling of the UCB**. Though rare, it is possible that incorrect labeling of an umbilical cord blood unit could occur so that your child receives the wrong unit. To avoid this, umbilical cord blood unit is re-typed to ensure that the tissue type of the donor and your child are as previously reported (i.e., when the donor unit is confirmed). If the umbilical cord blood unit does not have an attached segment for us to re-type, there are several ways the unit labeling can be confirmed.

6. **Other Complications**. Other complications that can result from the transplantation procedure not specifically related to one specific drug or the cord blood stem cells or this study include:

   A. **Damage to the vital organs in your body.** This could result in problems in any body organ, such as, heart, lungs, liver, gut, kidneys and bladder, brain etc. The lungs and the liver are particularly vulnerable. Some patients will experience severe lung problems due to infections and/or due to a reaction of the lungs to the chemotherapy and radiation. Some patients can suffer veno-occlusive disease of the liver (VOD). This complication results from high doses of chemotherapy and/or radiation. Patients with VOD become jaundiced (yellowish skin), have liver function abnormalities, abdominal swelling, and abdominal pain. Although many patients recover completely, these complications may cause permanent damage or even death.

   B. **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, preventative 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.

   C. **Recurrence of disease.** Your child's leukemia or MDS may come back even if the transplant is initially successful.

   D. **Risk to the unborn.** The treatments in this study have NOT been proven to be safe at any stage of pregnancy. Therefore, if your child is pregnant or nursing, your child is not eligible for this study. Women who have the potential of becoming pregnant must use some form of effective birth control while receiving chemotherapy, TBI and GVHD prophylaxis. Effective birth control is defined as the following: 1) refraining from all acts of vaginal intercourse (ABSTINENCE); 2) consistent use of birth control pills; 3) injectable birth control methods (Depo-Provera, Norplant); 4) tubal sterilization or male partner who has undergone a vasectomy; 5) placement of an IUD (intrauterine device); and, 6) use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.

   E. **Sterility and future childbearing potential for men and women.** Chemotherapy and/or irradiation may affect your child's ability to have children. Male patients are likely to become sterile (unable to produce sperm) and should discuss with their doctor regarding sperm banking prior to transplantation. Female patients who have attained puberty may find that their menstrual cycle becomes irregular or stops permanently. However, this DOES NOT MEAN THAT YOUR CHILD CANNOT BECOME PREGNANT, and your child must use some effective method of birth control (if she has a sexual partner) during transplant and afterwards until she is off GVHD prophylaxis. Damage to reproductive tissue may result in infertility (inability

to have children). It is not known if the damage could result in birth defects. You and your child should discuss these risks and options in detail with your child's doctor before entering this study.

F. **Central venous catheter.** Central venous catheters are intravenous (IV) lines that are placed under the skin and in a large vein in the chest and which may remain in place for many months. Central venous catheters are used to draw blood and administer fluids and medicines. There is considerable experience with central venous catheter use. The most common complications associated with central venous catheters are blood clots in the catheter and an infection where the catheter was inserted which can sometimes lead to a generalized infection in the blood. Clotting may require the catheter to be removed or treatment with a fibrinolytic agent (medicines that dissolve blood clots). Sometimes if a blood clot occurs, the catheter may need to be replaced. Infections will be treated with drugs; sometimes, removal of the infected catheter is required and a new catheter will be placed. There is also a small risk of puncturing the lung at the time the catheter is put in. If this occurs, a temporary chest tube may be placed in the lung to re-inflate it. There are no long-term effects once the lung puncture has repaired.

What are the costs of taking part in this study?
Most of what happens 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, the radiation therapy, the drugs, and the cost of the umbilical cord blood unit(s). There will be no charge for research tests. 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.

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

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Members of the Blood and Marrow Transplant Clinical Trials Network, which is conducting this study
- The EMMES Corporation, a research organization that is helping to coordinate this study
- The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research, 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 Children's Oncology Group (COG), a clinical trials cooperative group

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.

HIPAA[1] 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 *Multi-Center, Open-Label, Randomized Trial Comparing Single Versus Double Umbilical Cord Blood (UCB) Transplantation in Pediatric Patients with High Risk Leukemia and Myelodysplasia.*

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.

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)

_____

_____

_____

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 #0501 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)

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

- 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
- Cord Blood Banks providing units
- Children's Oncology Group, a clinical trials cooperative group
- Other:

_____

_____

_____

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.

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Storage of blood for future research:

Please note: This section of the informed consent form is about future research studies that will be done using blood samples from children who are taking part in the main study described above. Your child may give samples for these future research studies if you want to. You can say "yes" or "no" to allowing blood samples for future research studies. You can still be a part of the main study even if you say 'no' to allowing these samples to be used for future research studies. Please mark your choice at the end of this section.

Your child will be asked to provide samples of blood to be used for research to determine how the immune system is recovering after transplant. These samples will not require additional procedures. The samples will be taken from blood drawn normally for other tests and will not require additional needle sticks. Your child's name will not be on these samples. You do not have to agree to provide these research samples from your child in order for your child to participate in the study.

Samples will be labeled with unique codes that do not contain information that could identify your child. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the laboratories where your samples are being tested do not have a link to this code. Your samples will be stored at these laboratories until the entire sample has been used for the research tests or until the end of the study.

If you agree, we will collect your child's (your) blood at Day 100, 6 months, 12 months and 24 months after transplant (approximately 15 mL, 1 tablespoon, each time) for immune recovery studies.

Things to think about regarding use of blood for immune recovery studies:
The choice to let us have a blood samples for immune recovery studies is up to you (and your child). No matter what you decide to do, it will not affect your child's care. Even if you decide now that your child's blood sample can be kept for studies, you (or your child) can change your mind later. If this is the case, tell us that you are no longer interested in allowing us to use your child's blood sample for research. We will then destroy the blood samples.

Benefits: The benefits of research using blood include learning more about what causes cancer and other diseases, what causes complications after transplantation and how to prevent and how to treat them.

Risks: The main risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice: Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

- ❑ Yes, I agree to allow my child's blood used for future research.
- ❑ No, I do not agree to have my child's blood used for future research.

_____ _____
Signature *Date*

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)

_____ _____
Signature of Physician Obtaining Consent *Date*

_____
Printed Name of Physician Obtaining Consent

ASSENT FORM

Multi-Center, Open-Label, Randomized Trial Comparing Single versus Double Umbilical Cord Blood Transplantation in Pediatric Patients with High-Risk Leukemia and Myelodysplasia

You have leukemia. Leukemia is cancer of the blood cells made in your body's "blood factory", which is called the bone marrow. Leukemia is treated with special medicines. These medicines are called chemotherapy. They kill cancer cells. If chemotherapy doesn't kill all of the cancer cells, a special and stronger treatment called a transplant may be needed.

During a transplant, you get a very large amount of chemotherapy medicines and radiation therapy. These kill the leukemia in your body. The chemotherapy drugs you will receive are so strong that they also kill the normal cells in your blood and bone marrow. To make your bone marrow grow new, healthy cells, you are given a transplant from a donor. The cells in the transplant travel to your bone marrow and grow new cells. Your doctors think that a transplant is the best treatment for you. They believe that it will increase your chance of cure.

Cells from the donor's bone marrow or cord blood can be used in a transplant. Bone marrow cells are donated by volunteers. Bone marrow donors have to have the same kind of bone marrow as the patient. If your doctor cannot find a bone marrow donor for you, you can be transplanted with blood cells from a baby's umbilical cord. Umbilical cord blood is the extra blood left over after a baby is born. It used to be thrown away. We know now that it contains blood-forming cells like the ones found in bone marrow. Cord blood can be collected after a baby is born and stored for future use. Collecting cord blood does not hurt the baby or Mom. When a patient, like you, needs a transplant, cord blood can be removed from storage and sent to your hospital for your transplant. There have been many transplants using umbilical cord blood. Sometimes the transplants grow back too slowly or not at all. In this study, your doctors are trying to figure out if the transplant will grow back faster if blood cells from two umbilical cords are used instead of one umbilical cord. They don't know the answer. They need to do this study to find out whether two cord blood units are better than one.

If you agree to participate the following will occur:

1. Your doctor will check to make sure that there are two umbilical cord blood donors available for you.
2. Then a computer program will decide whether you will get one or two cord blood units. This is called randomization. Randomization is like flipping a coin. You have the same chance of receiving one or two cord blood units. By assigning treatment this way, your doctors will be able to learn which of these treatments is better.

Transplant Procedure

Before the transplant, you will be given the drugs cyclophosphamide and fludarabine. These drugs will be given through a central line – an IV that will be placed in your chest. If you do not already have a central line, we will put one in as a surgical procedure (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 or receive shots). You will also get radiation to your whole body twice a day for four days. After you have received these drugs and radiation, new blood cells from cord blood will be given through your central line. When the blood gets into your body, you may feel sick to your stomach but that will go away quickly. You will be in the hospital for about four weeks after the cord blood cells are given to you while we are waiting for the cord blood cells to grow up inside your body and for you to recover from the chemotherapy and radiation. You will need to be on a number of medications during your transplant, which will either be given through your line or will be taken by mouth.

It will be necessary to check your blood and bone marrow after the transplant to make sure the cord cells are growing in your body. Your doctors will do blood tests and bone marrow tests. Blood tests will also be done by taking blood through your line.

Risks/Discomforts
The drugs and radiation may cause hair loss, nausea and vomiting, and diarrhea. 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.

During the period your new bone marrow is growing back after the cord blood transplant, you may need to get antibiotics since you will not be able to fight infections. You may also need to get blood transfusions since your new bone marrow will not be making new blood cells right away. It is possible that your new bone marrow will not grow back. This is unlikely but if it did happen, it may even be necessary to do a second transplant. You may get graft-versus-host disease (GVHD), which happens when transplanted cells attack your body causing skin rash, vomiting, diarrhea and liver problems. These problems could be mild, or they could be very serious. Your doctors will do their best to make you feel better and keep you safe.

The above information has been explained to me. My questions have been answered.

I agree to participate in this study.

_____ _____
Patient Parent

_____
Physician

_____ _____
Witness Date