Informed Consent to Participate in Research

Your Name: _____

Study Title: Reduced-Intensity Conditioning for Children and Adults With Hemophagocytic Syndromes or Selected Primary Immune Deficiencies (RICHI)

Protocol: BMT CTN #1204

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Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. We are doing this study because we want to learn if **reduced-intensity transplants** are safe and work well for people with **hemophagocytic syndromes** or immune disorders. A reduced-intensity transplant uses lower doses of chemotherapy. This type of transplant is also called a non-myeloablative, or 'mini' transplant.

An **allogeneic transplant** uses cells from a family member or an unrelated donor to remove and replace your diseased cells. An allogeneic transplant generally uses higher levels of chemotherapy and radiation (also known as high intensity treatments or myeloablative conditioning regimens) to destroy the diseased cells before receiving the donor cells. However, high intensity transplants can have more side effects during and after transplant. A reduced-intensity transplant can have fewer side effects, but may have more problems with **engraftment**. Engraftment is the ability of the donor cells to replace the patient's cells.

Your study participation will last for **1 year** post-transplant. This study will take about 3 years total and will include 35 HLH patients in addition to patients with other hemophagocytic syndromes or immune disorders from around the United States and Canada.

To be part of the study, you must:

- Be between the ages of 3 months and 45 years
- Have a hemophagocytic syndrome or an immune disorder including:
  - Hemophagocytic lymphohistiocytosis (HLH)
  - Griscelli syndrome
  - Chediak-Higashi syndrome
  - X-linked lymphoproliferative disease
  - Chronic active EBV (CAEBV), which is typically associated with HLH
  - Chronic granulomatous disease (CGD)
  - X-linked hyper IgM syndrome (HIGM1)
  - IPEX syndrome
  - Severe leukocyte adhesion deficiency (LAD-I)
- Have a matched related marrow donor or unrelated marrow donor available. The unrelated donor needs to be a close tissue match.
- Provide a signed consent for participation in the study

This Consent Form tells you about the purpose of the study, the possible risks and benefits, other treatment options available to you, and your rights as a participant in the study. Please take your time to make your decision.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [*insert name of facility or institution*].
- Please ask the study staff questions about anything that you don't understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment options if you don't want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN will direct the research study. The BMT CTN and the NIH will make decisions about how to manage the study together.

Some of the immune system disorders included in this study are: Hemophagocytic lymphohistiocytosis, Griscelli syndrome, Chediak-Higashi syndrome, X-linked lymphoproliferative disease, chronic active EBV, chronic granulomatous disease, hyper IgM syndrome, IPEX syndrome, and severe leukocyte adhesion deficiency. These disorders prevent the immune system from working well. Your immune system fights off infections, so people with these disorders might develop deadly infections.

One way to treat these disorders is through a blood and bone marrow transplant. A transplant replaces your unhealthy blood cells with bone marrow cells from a family member or an unrelated donor. It requires a close tissue match between you and the donor. Your donor could be a sibling (a sister or brother) or an unrelated person. In the United States, we use the Be The Match® Registry to find unrelated donors.

A transplant first uses chemotherapy to destroy the unhealthy blood cells or stop them from growing. Then, we replace the destroyed cells with the new cells from your donor. In this study, doctors want to use lower doses of chemotherapy. This type of transplant is called a reduced-intensity transplant.

Your disease can be treated in other ways too. You and your doctor will decide on the best treatment for you.

3. Study Purpose

We are inviting you to join this study because you have an immune system disorder, a matched bone marrow donor, and a reduced-intensity transplant is a treatment option for you. The goal of this study is to learn if a reduced-intensity transplant is safe and works well to treat your disease. We also want to know how well your immune system responds to the transplant.

4. Right to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about the study or you want to leave the study, please contact:

[*insert contact info for site PI*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or to leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before your transplant. We will also check your health several times after your transplant for up to 1 year.

Before Your Transplant:

You will be admitted to the hospital 14 days before your transplant. Your doctor will put an intravenous (IV) catheter (a thin tube) in a large vein in your neck or chest. This is done to make giving you drugs and blood transfusions easier and less painful. This is also known as a central venous catheter.

When you are ready to get your catheter, your doctor will explain what will happen in more detail. Your anesthesiologist (the doctor who will give you pain medicine) will describe the risks and benefits of the pain medicine.

When the catheter is in your chest, it will need to be cleaned and flushed regularly to prevent infection and blood clots. Your nurse or caregiver will help you clean your catheter.

Reduced-Intensity Transplant:

To prepare your body for transplant and destroy the diseased cells, you will be treated with chemotherapy and other medicines. Your chemotherapy will start the day you are admitted to the hospital (14 days before your transplant).

Study chemotherapy drugs
The study drugs that will be used for your chemotherapy are called **alemtuzumab**, **fludarabine**, and **melphalan**.

We will start giving you alemtuzumab 14 days before your transplant. It will be given as a shot. You will get a dose of alemtuzumab once a day for 5 days. The first day will be a small test dose. The test dose is given to make sure you will not have a bad reaction to the full dose. If you have a bad reaction, your doctor will talk with you about other drug options to prepare for transplant.

The risks of alemtuzumab are listed in Section 6: Risks and Discomforts. These risks include serious allergic reactions. Patients are usually admitted to the hospital for their first dose of alemtuzumab. Your doctor will decide if you need to stay in the hospital for the other doses of alemtuzumab or if you can receive them as an outpatient.

If you stay in the hospital for all of the alemtuzumab shots, your doctor might discharge you after the shots are done if you respond well. If you are discharged, you will return to the hospital 8 days before your transplant to start receiving the other chemotherapy drugs (fludarabine and melphalan).

Fludarabine will be given through your central venous catheter, once a day for 5 days. A central venous catheter is a thin tube that is placed in a large vein in your neck or

chest. We will give you one dose of melphalan 3 days before the transplant. It will also be given through your central venous catheter.

You will have 2 days to rest before your transplant. We won't give you any chemotherapy drugs on these days.

Table 1 shows the timeline for the chemotherapy drugs and blood tests. This timeline does not show the drugs we will give you to help prevent Graft Versus Host Disease (below).

Drugs to prevent Graft-Versus-Host Disease (GVHD):
We will give you immune suppressing drugs 3 days before your transplant. We will continue to give you these drugs after your transplant. These drugs are important because they allow the donor cells to perform their new role in your body. They can also lower your chances of developing GVHD. GVHD happens when the donor cells attack your body (GVHD is discussed in more detail below).

You will receive 1 or more standard drugs (drugs that are not part of the study) to lower your chances of developing GVHD. We will give you these drugs for at least 6 months after the transplant. They are cyclosporine (also called Gengraf® or Neoral®) or tacrolimus (also called FK 506 or Prograf®). We will give them to you with methylprednisolone or prednisone daily starting 2 days prior to transplant and continuing until 28 days after transplant (both of these drugs work the same).

Donated marrow cells:
The donated marrow cells will come from a related donor or unrelated donor. The donor cells will be given through your catheter, just like a blood transfusion.

After Your Transplant:

The chemotherapy drugs will destroy the cells in your bone marrow that produce your blood and immune cells. The donor cells will produce new blood cells in your body. To speed up this process, we may give you a drug called Filgrastim (also called G-CSF or Neupogen). This drug helps protect against infections. It is given as a shot or IV.

Check-up appointments:
You will stay in the hospital after your transplant until your doctor feels you're well enough to go home. When you're in the hospital, we will watch you carefully for signs of infection and other problems. A physical exam and blood tests will be done every day to know how you're doing. Your doctor may need to give you other drugs, tests and treatments if you have problems.

After you leave the hospital, you will need to visit the transplant clinic at least once a week for check-ups to make sure you're still doing well. You will also need to visit us 100 days (3 months), 6 months, and 1 year after your transplant so we can check your progress and treat any problems. You will check in with us less and less over time.

At these visits, we will take 2 – 6 teaspoons of your blood (10 – 30 mL) from your catheter or from a vein in your arm if your catheter has been removed. We will test your blood to see how well your body is responding to the chemotherapy drugs and the donated cells.

Health Evaluations:

We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They would be done even if you were not part of this study.

Health evaluations after treatment:

1) Physical exam to assess toxicities, and infections weekly until Day +56 and then at Days +180 and +365.

2) Physical exam to assess GVHD weekly until Day +100 and then at Days +180 and +365.

3) Routine blood tests (cell counts and liver and kidney function) weekly until Day +56 and then at Days +180 and +365.

4) Blood or bone marrow tests to find the amount of donor cells in your body monthly until Day +100 and then at Days +180 and +365. This is also called *chimerism*.

5) Disease-specific tests to see how much disease you have before treatment and after treatment on Days +100 and +365.

6) Optional blood samples for future research (see **Section 17: Blood Samples for Future Research**).

Your doctor may decide that you need other tests and treatments that are not part of this research study, but are necessary to take care of you.

Table 1: Timeline for Chemotherapy Drugs and Blood Tests

Day:	Before transplant															Transplant Day	After transplant							
	After you consent	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0	1	14	28	42	70	100 (3 mths)	180 (6 mths)	365 (1 yr)
Optional Blood Tests:	✓								✓						✓		✓	✓	✓	✓	✓	✓	✓	✓
Drugs*:		A	B	B	B	B		C	C	C	C	C	D											

***Legend for Chemotherapy Drugs**

A	Alemtuzumab test dose
B	Alemtuzumab
C	Fludarabine
D	Melphalan

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to very serious.

The risks listed in this section might happen from transplant. These risks might happen if you have a transplant as part of this study or standard care. The chances of developing GVHD and infections are the same if you have a reduced-intensity or standard transplant.

Your doctor will give you drugs to help lower the side effects, such as feeling sick to your stomach (nausea). In some cases, side effects can be long lasting or may never go away.

The chemotherapy drugs can cause leukemia years later, but this is rare. These "secondary cancers" are often very hard to treat and can cause death.

Risks of Study Treatments and Drugs

Likely	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Possible Side Effects of Study Drugs

The most common side effects of the treatments used in this study are listed below. There is also the risk of very uncommon or unknown side effects. All chemotherapy drugs in this study are commonly used in transplant.

Alemtuzumab		
Likely	**Less Likely**	**Rare, but Serious**
• Fever • Chills • Anemia (decreased number of red cells) • Infection • Bleeding • Weakened immune system • Local irritation (skin) at injection site • Low number of white blood cells • Low number of platelets in the blood	• Nausea • Vomiting • Diarrhea • Rash • Headache • Sweating • Back pain • Severe itching • Allergic reaction of skin and blood vessels • Tiredness • Loss of appetite • Low blood pressure • Irregular heartbeat • Shortness of breath • Sore throat • Pain • Cough	• Abdominal pain • Dizziness • High blood pressure • Blisters • Pain in the muscles • Herpes simplex infection • Swelling of the throat • Bacterial infection in the bloodstream

Fludarabine		
Likely	**Less Likely**	**Rare, but Serious**
▪ Infection ▪ Anemia (low red blood cell count) ▪ Tiredness ▪ Nausea ▪ Vomiting ▪ Pneumonia ▪ Mouth sores ▪ Fever ▪ Swelling of hands and feet ▪ Weakened immune system ▪ Pain ▪ Low number of white blood cells ▪ Low number of platelets in the blood ▪ Electrolyte imbalances	▪ Diarrhea ▪ Numbness and tingling in hands and/or feet ▪ Changes in vision ▪ Skin rash ▪ Cough ▪ Changes in heartbeat ▪ Loss of appetite ▪ Chills ▪ Lung inflammation	▪ Changes in vision ▪ Agitation/nervousness ▪ Confusion ▪ Difficulty breathing ▪ Weakness ▪ Severe brain injury and death ▪ Bleeding due to decreased numbers of platelets ▪ Kidney damage that could require dialysis ▪ Coma

Melphalan		
Likely	**Less Likely**	**Rare, but Serious**
▪ Loss of appetite ▪ Nausea ▪ Vomiting ▪ Skin breakdown (if drug leaks from vein) ▪ Anemia (low red blood cell count) ▪ Infection ▪ Bleeding ▪ Mouth sores ▪ Temporary hair loss ▪ Decreased immunity ▪ Low number of white blood cells ▪ Low number of platelets in the blood	▪ Diarrhea ▪ Inflammation of the lung ▪ Weakness ▪ Weight loss	▪ Low blood pressure ▪ Excessive perspiration ▪ Allergic reaction ▪ Damage/scarring of lung tissue ▪ Sterility ▪ Seizure ▪ Cancer of bone marrow cells ▪ Heart stops beating ▪ Liver damage

Side Effects of Drugs Used To Prevent GVHD

The side effects of the GVHD drugs (listed below) usually stop when you're done taking them.

Cyclosporine (Gengraf® or Neoral®).

This drug may be used for all patients

Likely	Less Likely	Rare, but Serious
▪ Tremors ▪ High blood pressure ▪ Kidney problems ▪ Headaches ▪ Nausea ▪ Vomiting ▪ Stomach pain or indigestion ▪ Swelling of the hands or feet ▪ Increased hair growth ▪ Electrolyte imbalances	▪ Confusion ▪ High levels of triglycerides in the blood ▪ Diarrhea ▪ Gum enlargement ▪ Liver dysfunction ▪ RPLS/PRES[1]	▪ Muscle cramps ▪ Numbness and tingling of the hands or feet ▪ Seizures ▪ Dizziness ▪ Red blood cell destruction ▪ Temporary blindness

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) – See text below for description

Tacrolimus (Prograf® or FK-506)

This drug may be used for all patients.

Likely	Less Likely	Rare, but Serious
▪ High blood pressure ▪ High blood sugar ▪ Anemia (low red blood cell count) ▪ High or low potassium levels ▪ Low magnesium and calcium levels ▪ Loss of appetite ▪ Diarrhea ▪ Nausea ▪ Fever ▪ Headache	▪ Hair loss ▪ Vomiting ▪ Tingling sensation in the extremities ▪ Itching ▪ Rash ▪ Abdominal pain ▪ RPLS/PRES[1]	▪ Confusion ▪ Painful joints ▪ Increased sensitivity to light ▪ Change in vision ▪ Insomnia (trouble sleeping) ▪ Infection ▪ Jaundice (skin yellowing) ▪ Kidney injury ▪ Seizures

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) – See text below for description

Methylprednisolone and Prednisone

This drug will be used as part of GVHD prophylaxis for bone marrow recipients.

Likely	Less Likely	Rare, but Serious
▪ Water retention (storing of extra water) ▪ Overeating ▪ Weaker immune system ▪ Temporary personality changes ▪ Abnormal hormone production ▪ High blood sugar ▪ Slowed growth ▪ Decreased bone density ▪ Fat accumulation causing a change in facial appearance	▪ Headaches ▪ Poor wound healing ▪ Stomach swelling or pain ▪ Tissue swelling ▪ High blood pressure ▪ Stomach ulcer ▪ Muscle weakness ▪ Cataracts ▪ Bone cell death ▪ RPLS/PRES[1]	▪ Difficulty falling asleep ▪ Worsening of diabetes ▪ Inflammation of pancreas ▪ Personality disturbances ▪ Bleeding in the stomach and intestines ▪ Increased pressure within the eye ▪ Disturbance of bone calcium (might lead to possible broken bones or permanent bone damage)

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) – See text below for description

Filgrastim (G-CSF)		
Likely	**Less Likely**	**Rare, but Serious**
▪ Ache or pain inside the bones ▪ Increased levels of liver enzymes and uric acid in the blood ▪ Low number of platelets in the blood ▪ Headache ▪ Tiredness	▪ Local irritation (skin) at injection site ▪ NauseaBleedingFever	▪ Allergic reaction ▪ Enlargement or rupture of the spleen ▪ Worsening of pre-existing skin rashes ▪ Temporary hair loss ▪ Inflammation of a blood vessel in the skin

Potential Risk of RPLS/PRES

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

The DSMB has noted that patients transplanted on the clinical trial BMT CTN 1204 have a higher than expected occurrence of a usually uncommon (<5%) complication called reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES). Patients with RPLS/PRES have confusion and other changes in their ability to think. Sometimes, they experience seizures, sleepiness or, rarely, loss of consciousness. RPLS is diagnosed with an MRI of the brain. 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. Three out of thirty-five patients on BMT CTN 1204 have developed RPLS/PRES; all were successfully treated for this complication. Thus far, no RPLS/PRES has been observed in any patient more than 6 months from their date of transplant. We believe that children who are on prednisone or other corticosteroids, or immunosuppressive drugs such as cyclosporine or tacrolimus or have high blood pressure are more likely to develop RPLS/PRES.

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

Risks of Transplant:

The following problems might happen from your transplant. These problems might happen if you have a transplant as part of the study or standard care:

Graft-versus-host disease (GVHD)
GVHD develops when the white blood cells, which are called T cells, in the donor's cells attack your body. You are more likely to get GVHD if your donor's tissue does not closely match your tissue.

There are 2 kinds of GVHD: acute and chronic. Acute GVHD usually develops in the first 3 months after transplant. Chronic GVHD usually develops later and lasts longer.

You may experience these side effects with acute GVHD:

- Skin rash
- Feel sick to your stomach (nausea)
- Throw up (vomit)
- Diarrhea
- Abdominal (stomach area) pain
- Problems with your liver (your doctor will run tests for this)
- Infection

You may experience these side effects with chronic GVHD:

- Skin rashes
- Hair loss
- Thickened skin
- Joint stiffness (knees, elbows, fingers)
- Dry eyes
- Dry mouth
- Liver disease (your doctor will run tests for this)
- Weight loss
- Diarrhea
- Infection

We don't know for sure if you will develop acute or chronic GVHD. The chance that you will get GVHD is 10-30%. This means that 10 to 30 people out of 100 might develop it. We will watch you closely for GVHD and treat it if it happens.

To know for sure if you have acute or chronic GVHD, we may do a biopsy of your skin. A biopsy is where we take a small piece of your skin and look at it under a microscope for signs of GVHD. There's a small chance that we might also do a biopsy of your intestine and liver. Risks of biopsy may include pain, infection, or bleeding.

In most cases, GVHD can be treated. If GVHD does not respond to the drugs, your doctor will talk with you about other treatment options. If you choose a different treatment option, we will give you information about the side effects.

You may need to be treated for GVHD for many months or years. GVHD treatments can cause your immune system to become very weak if it goes on for a long time. This means you may develop more infections and need to be admitted to the hospital often. GVHD can be very serious and hard to treat. It might also cause death.

Damage to your vital organs

Your vital organs include your heart, lungs, liver, intestines, kidneys, bladder and brain. The chemotherapy and GVHD drugs may hurt these organs. You may develop lung problems from chemotherapy or an infection.

Some patients can have veno-occlusive disease (VOD) of the liver even from a reduced-intensity transplant (lower doses of chemotherapy). Patients with VOD become jaundiced (yellow skin), have problems with their liver, retain too much water (feel swollen and uncomfortable), and have stomach swelling and pain.

If there is serious damage to your vital organs, you may have to stay in the hospital longer or return to the hospital after your transplant. Many patients get better, but these complications can cause permanent damage to your organs or death.

Serious infections

It may take many months for your immune system to recover from the chemotherapy and GVHD drugs. There is an increased risk of infection during this time when your body is healing. We will give you drugs to reduce the chance of infections, but they may not work. If you have an infection, you may have to stay in the hospital longer or return to the hospital after transplant. Many patients get better, but some infections can cause death.

Graft (donor cells) rejection

Some patients' bodies reject the donor cells (graft) with a standard (non-reduced-intensity) transplant. There is an increased risk of rejection with a reduced-intensity transplant. Also, a certain amount of your old blood and marrow cells will remain in your body.

If your body rejects the donor cells, your doctor may need to give you a donor lymphocyte infusion (DLI). A DLI is an extra dose of the donor cells. You may also get another transplant, but this is rare. If you need a DLI or second transplant, your doctor will explain the risks and benefits.

Central venous catheter

You may feel pain and bleed a little where the catheter is placed in your chest. The most common risks of a catheter are blood

clots and infections. If you get a clot, we will give you a drug to break it up. If the drug doesn't work, the catheter may need to be replaced. Infections will also be treated with drugs. Sometimes, the catheter has to be taken out and a new catheter put in. Also, the catheter could puncture (create a hole) in your lung and cause serious bleeding, but this is very rare.

We will do an X-ray or CT scan of your chest to make sure we know the best place to insert the catheter and reduce the risks from happening as much as possible.

Infertility and reduced sexual functioning
Chemotherapy can cause infertility (inability to have children). It may decrease your sexual desire and cause female vaginal dryness.

The chemotherapy doses used in this study are lower than what is used in standard transplants, so the risk of infertility may be lower. Some patients who received reduced-intensity transplants had children. It's difficult to know the exact risk of infertility from reduced-intensity transplants. We don't know for sure what your risk of infertility will be.

Risk to the unborn

The treatments in this study have not been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who can become pregnant must use two forms of effective birth control while receiving chemotherapy and drugs to prevent GVHD. Effective birth control is defined as the following:

1. Refraining from all acts of vaginal sex (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)
6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children or possibly cause birth defects if you take them while you are pregnant. It is important that a woman is not pregnant or breast-feeding and does not become pregnant during the course of the study.

If you are a woman and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use an effective method of birth control during

your transplant and continue until you are finished with your GVHD prevention treatment.

If you are a man, your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant.

Please check with your doctor to understand more about these risks.

Risk of death
The side effects of a blood and bone marrow transplant might be very serious and cause death. Your doctor will do everything to make sure your transplant is as safe as possible, but there is still a risk of death.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive a blood or marrow transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant
- A blood or marrow transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood disorder at this time
- Comfort care: This can occur at any stage of a disease. The goal is to make you comfortable by treating symptoms of the disease and improving your quality of life. You may still be receiving treatment for your disease. This is different from hospice care.

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

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

8. Possible Benefits

We don't know if taking part in this study will make your health better. If the transplant works well, you may not have any more symptoms of your disorder. The information from this study will help doctors learn if reduced-intensity transplants are safe and work well for people with hemophagocytic syndromes or immune disorders.

9. New Information Available During the Study

During this study, the study doctors may learn new information about the study drug or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer take part in the study, or that you may not want to continue in the study. If this happens, the study doctor will stop your participation and will offer you all available care to meet your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information 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 about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- /Institution/
- The National Institutes of Health (NIH)
- The National Heart, Lung, and Blood Institute (NHLBI)
- The National Cancer Institute (NCI)
- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)
- Institutional Review Boards (IRBs) responsible for this study
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- Study investigators

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at:

www.ClinicalTrials.gov. Federal law requires study information for certain studies to be submitted to the data bank.

For questions about access to your medical records, please contact /name/ at /number/.

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

You could have serious health risks if you stop treatment during the conditioning process before you receive your transplant. If you stop taking the immune suppressing drugs (see **Section 6: Risks and Discomforts**) too soon after transplant, your body could reject the donor stem cells or you could develop serious complications and possibly die.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

If you decide to leave this study after the study, or your doctor asks you to leave the study for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study results.

12. Physical Injury as a Result of Participation

It is important to tell your study doctor, _____ *[investigator's name(s)]*, or study staff if you feel that you have been injured from taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to receive payment by signing this Consent Form.

13. Compensation or Payment

You will not be paid for taking part in this study. You will not be compensated or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

14. Costs and Reimbursement

Most of the tests for this study are standard medical care for your transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for tests that are only done for research on this study. You will not pay for any extra tests that are being done for the study.

Some health plans will not pay the costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[Insert name and contact detail]

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about the project, or any questions about your rights as a research participant, then you may contact:

[Insert appropriate contact details]

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

For questions about your 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 rights) at _____ telephone number).

17. Blood Samples for Future Research (Optional)

This section of the informed consent form is about future research studies that will use blood samples from people who are taking part in the main study. You may choose to give blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give blood samples for future research studies.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide blood samples, here is what will happen:

a) We will collect 11 extra blood samples from your catheter or by a vein in your arm at the same time you have routine blood tests done **(Table 1)**. We will take about 4 teaspoons (20 mL) of your blood each time. If you weigh less than 6.7 kg, the amount of blood will be based on your weight (3 mL/kg).

   We will collect your blood on these 11 days:

   - After you consent to giving blood samples, but before you start the chemotherapy drugs
   - 7 days and 1 day <u>before</u> transplant
   - 1, 14, 28, 42, 70, 100, 180, 365 days <u>after</u> transplant

b) The blood samples for future research will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. Only the repository will have the link between you and your research samples. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples.

c) Samples stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.

d) Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

e) DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH).

Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples although the results of genetic studies could theoretically include identifying information about you.

Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is small, but may grow in the future. Researchers have a duty to protect your privacy and to keep your information confidential.

Some general things you should know about letting us store your blood for research are:

- We will only store samples from people who give us permission.
- Research is meant to gain knowledge that may help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.
- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.
- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

You can change your mind at any time about allowing us to use your samples and health information for research.

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

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.

Statement of Consent for Future Research Samples

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

The decision of whether to allow us to use the samples for future research and for your genetic code to be released onto a public database is completely up to you. There will be no penalty to you if you decide not to allow this, and your decision will in no way affect your participation in this research.

If you agree to allow your samples to be used for future research you also agree to have your genetic code released to a public database and made accessible to other researchers.

❑ I agree to allow my blood samples to be stored for future research.

❑ I <u>do not</u> agree to allow my blood samples to be stored for future research.

_____ _____

Signature Date

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 individual health information for the purpose of conducting the research study entitled *Reduced Intensity Conditioning for Children and Adults with Hemophagocytic Syndromes or Selected Primary Immune Deficiencies.*

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 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 Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by my child (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 #1204 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 (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR)
- 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

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

_____

_____

_____

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 my child (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 for 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 need more information about this study, ask the study doctor.

TITLE: Reduced-Intensity Conditioning for Children and Adults with Hemophagocytic Syndromes or Selected Primary Immune Deficiencies (RICHI)

PROTOCOL NUMBER: BMT CTN #1204

PRINCIPAL INVESTIGATOR(S):

Name:

Address:

Email:

Phone:

Fax:

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____
Participant Name Date

_____ _____
Signature Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____ _____
Name of Counseling Physician Date

_____ _____
Signature of Counseling Physician Date

Pediatric Assent to Participate in Research

For Children Ages 7 to 17 years old

Study Title: Reduced-Intensity Conditioning for Children and Adults with Hemophagocytic Syndromes or Selected Primary Immune Deficiencies

Protocol: BMT CTN 1204

A. Why am I here?

We are inviting you to join our study because you will receive a bone marrow transplant to treat your disease. A transplant uses blood-making cells from another person (donor) to replace your cells that are not healthy. A donor is the name for a person who gives some of their blood-making cells for a transplant.

B. Why are you doing this study?

We want to learn if transplant works to cure your disease.

C. What will happen to me?

Before your transplant, you will have check-ups with the study doctors. Then, 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 and less painful for drawing blood for tests.

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 donor can be your sister or brother (related) or someone you don't know (unrelated). 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 your body attacks the donor cells. 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 don't know if the study will help you or not.

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 about other ways to treat your disease.

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.

Signature of Child	Date
Print Name 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.

Counseling Healthcare Professional	Date