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Informed Consent to Participate in Research

Fred Hutchinson Cancer Center
University of Washington Medical Center
Seattle Children's Hospital

BMT CTN 1904
Hematopoietic Cell Transplantation Using Treosulfan-Based Conditioning for the Treatment of Bone Marrow Failure Diseases

Your Name: _____

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Funding Sponsor: This study is funded by the National Institutes of Health, through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

Regulatory Sponsor: Fred Hutchinson Cancer Center

The ethics of this study have been reviewed and approved by the NMDP Institutional Review Board.

Your study doctor or nurse will review this **Consent Form** with you, including:

- ✓ The purpose of the research
- ✓ Possible risks and benefits
- ✓ Other options available to you
- ✓ Your rights if you join the study

1. Study Overview

We invite you or your child ("you") to join this clinical trial, also known as a research study. We're doing this study to see if the drug treosulfan with the drugs fludarabine and rabbit antithymocyte globulin (rATG) given before a blood or marrow transplant (BMT) will cause fewer complications and result in a more successful BMT than the standard of care chemotherapy without treosulfan.

You're being asked to join because you have a bone marrow failure disorder that can be treated with a BMT.

An **allogeneic BMT** uses healthy blood-forming cells from a donor to replace unhealthy ones. An allogeneic BMT is a treatment option for you because you have a bone marrow failure disorder. First, you will receive chemotherapy. Then, on the day of transplant you'll receive the donated blood-forming cells from your donor through your central venous catheter. You will also receive drugs to help prevent side effects and complications.

If you join this study, you will:

- Be in the study for about 1 year after your transplant.
- Receive 3 medicines (treosulfan, fludarabine, and rATG) as chemotherapy to prepare your body for a BMT
- Receive a BMT (blood-forming stem cells from a donor)

Some possible risks and benefits of joining the study include:

Possible Risks: You may have side effects from the drugs, including treosulfan. The bone marrow disorder may come back after BMT, and you may have serious side effects, like graft-versus-host disease (GVHD). GVHD happens when the donor's cells attack the cells in your body. There are many potential risks of having a bone marrow transplant as listed later in this consent regardless of enrollment on this research study.

Possible Benefits: You may have less severe complications after BMT than if treated with standard drugs, not including treosulfan. The BMT may cure the bone marrow failure disorder or treat it for some time.

If you do **not** join the study, you have other treatment options, such as:

- A BMT using different medicines to prepare your body for BMT
- Joining another clinical trial, if available (check with your doctor)
- Treating symptoms of the bone marrow failure disorder
- No treatment

Key points:

- Being in this research study is your choice.
- You may or may not benefit from being in the study. Knowledge gained from this study may help others.
- If you join the study, you can quit at any time. If you decide to quit the study, it will not affect your care at.the study site.
- Ask the study staff questions about anything you do not understand, or if you would like more information. You can ask questions now or any time.
- Take time to talk about the study with your doctor, study staff, and your family and friends. It is **your** choice to be in the study. If you decide to join, please sign at the end of this Consent Form. You will get a copy to keep. No one can force you to join this study.

2. Study Purpose

We are doing this study to find out if the drug treosulfan, given with fludarabine and rATG as the conditioning regimen before a blood or marrow transplant (BMT) will cause fewer complications and result in a more successful BMT than the standard of care conditioning regimen without treosulfan.

In the past, patients with bone marrow failure disorders often had poor outcomes after a BMT. These patients had a high risk of organ damage from the chemotherapy (and radiation, if used) in the conditioning regimen. As well, sometimes the transplanted bone marrow cells did not take and grow into healthy blood cells, causing graft rejection.

Treosulfan is a chemotherapy drug. In Europe, it has been used as part of the conditioning regimen before a BMT for almost a decade. In the United States, it has been used in clinical trials for patients with bone marrow failure diseases undergoing a BMT for several years. The results of these studies using treosulfan show that it causes less damage to organs and yet is strong enough for the transplanted cells to grow.

Treosulfan has not been approved by the U.S. Food and Drug Administration (FDA) as there needs to be more clinical trial results to confirm that it is a safe and effective chemotherapy drug to use in BMT. This research study is registered with the FDA, and they will monitor this study.

This is a phase 2 study. Studies in this phase test how well a new treatment will work to treat a disease.

3. Study Treatment and Tests

Before Your Treatment

You'll need to have several tests to see if you can be in the study. These tests are part of your regular care. They would be done even if you decide not to join this study. The tests include:

- Medical history
- Physical exam, including height and weight
- Blood tests, including HLA typing
- Bone marrow biopsy
- Chest X-ray or CT scan
- ECHO or Echocardiogram (Heart ultrasound)
- Liver scan if you've had a lot of red blood cell transfusions
- Lung function tests
- Kidney function tests
- Pregnancy test, if you're female and can get pregnant
- Urine test

During the Study

If you join the study, here is what will happen:

First, you will receive drugs (chemotherapy) through your central venous catheter to prepare your body for BMT. This step is called the conditioning regimen. These drugs also help the donor cells engraft. "Engraft" means that the cells start to grow and make new cells and show up in your blood.

These drugs include:

1. Treosulfan – a chemotherapy drug given each day for 3 days, starting 6 days before BMT (Day -6 though Day -4)
2. Fludarabine – a chemotherapy drug given each day for 5 days, starting 6 days before BMT (Day -6 through Day -2)
3. Rabbit ATG (rATG) – proteins that help the donated cells grow in your body and help prevent complications. Given each day for 3 days, starting 4 days before your transplant (Day -4 though Day -2)

Table 1: Conditioning Regimen	
Days before BMT	**Treatments given as intravenous (IV) infusions through your central venous catheter**
6	Treosulfan and fludarabine
5	Treosulfan and fludarabine
4	Treosulfan, fludarabine, and rATG
3	Fludarabine and rATG
2	Fludarabine and rATG
1	None
Transplant Day	Infusion of blood-forming cells from a donor

Then, on the transplant day (Day 0), you will receive your donor cells (either bone marrow or peripheral blood stem cells) through your central venous catheter similar to a transfusion of red blood cells.

After Your Treatment

You will receive standard drugs to help prevent a complication called graft-versus-host disease, or GVHD. **GVHD** occurs when the donor cells see your body as foreign (or different) and attack it. It can be a very serious life-threatening side effect of transplant.

1. Tacrolimus – given every day through your central venous catheter, then switched to a pill or liquid that you take two or three times a day by mouth once you are able, for about 180 days after BMT.
2. Methotrexate – given as an infusion through your central venous catheter on days 1, 3, 6 and 11 after the BMT.

Your doctor may decide to give you other medicines throughout the study to help with any side effects or discomfort.

You will also need several tests after BMT to see how your body is doing with the treatment. These tests are part of regular care for patients who have had a BMT. They would be done even if you were not part of this study. You will have tests for at least a year after transplant as outlined in Table 2 below.

- Blood tests
- Bone marrow tests
- ECHO or Echocardiogram (Heart ultrasound)
- Liver tests
- Lung function tests
- Physical exam

Your Research Results

Your doctor may share some of your research results with you but not necessarily all of them. Your doctor will share any results with you if they show that you need new treatment or need to change your treatment. If you would like to see specific results, ask your doctor.

Timeline and Participants

This study will take about 4 years to complete and will include 40 people.

Table 2. Timeline of Study Tests

	Before BMT	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84	Day 91	Day 100	Day 180	Day 365
Health history, physical exam, & weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GVHD evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chimerism (donor) testing	X					X										X	X	X
Tests for infection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Bone Marrow Evaluation	X																	X
Disease evaluation	X																	X

4. Risks and Benefits

Possible Benefits

Taking part in this study may or may not make your health better. If it works for you, you may have less severe complications after BMT. The information from this study could help future patients with similar disorders also have less severe complications after BMT. BMT may cure the bone marrow failure issues associated with your bone marrow failure disorder or treat it for some time.

Possible Risks

You may have side effects during the study. Your bone marrow failure disorder may come back after BMT. Side effects can range from mild to severe and can even be life-threatening. Your health care team may give you medicine to help with certain side effects, like an upset stomach. In some cases, side effects can last a long time or may never go away.

Risks of Medicines

Table 3: Treosulfan Side Effects in Children

Very Common (10% or Greater)	Common (1% - 9%)	Uncommon/rare/unknown frequency
Abdominal pain	Abnormal creatinine (kidney function test)	Bleeding in the eye
Abnormal liver tests	Anal inflammation	Blistering of the skin
Anemia (low red blood cell count which can lead to fatigue)	Chills	Burning or prickling sensation on the skin
Diarrhea	Darkening of the skin	Capillary leak syndrome (tissue swelling) which can lead to dangerously low blood pressure
Fever	Difficulty swallowing	Cerebral hemorrhage (bleeding in the brain)
Hair loss	Headache	Constipation
Hepatotoxicity – damage to the liver including abnormal liver tests (not related to venoocclusive disease/sinusoidal obstruction syndrome)	Hives	Decreased appetite
Infections (bacterial, viral, fungal)	Mouth or throat pain	Diaper rash

Table 3: Treosulfan Side Effects in Children		
Very Common (10% or Greater)	**Common (1% - 9%)**	**Uncommon/rare/unknown frequency**
Itching	Nosebleeds	Dry eye
Low platelet counts which increases the risk of bleeding	Rash	Edema (swelling due to retention of fluids)
Low white blood cell count which increases the risk of infection	Redness of skin	Enlarged liver
Mucositis/stomatitis (painful inflammation/sores of the lips and lining of the mouth which may cause difficulties eating)	Severe rash with sores and/or peeling of the skin	Excess fluid in body cavity that surrounds the lung
Nausea	Skin pain	Feeling weak or tired
Vomiting (throwing up)		Hand-foot syndrome (redness, swelling, and pain on the palms of the hands and/or soles of the feet)
		Hematuria (blood in urine)
		High blood pressure
		Hypoxia (decrease in the amount of oxygen reaching the tissues)
		Indigestion
		Inflammation of the bladder
		Less acid than normal in the blood
		Low blood pressure
		Lung failure or pneumonia requiring oxygen therapy or mechanical ventilation
		Pain
		Pain in extremities
		Penile pain
		Pericardial effusion (fluid around the heart)
		Proctitis (rectal inflammation)
		Pulmonary hemorrhage (bleeding within the lungs)
		Seizure
		Severe inflammation of the colon
		Severe loss of kidney function which may require artificial kidney machine
		Skin ulcer
		Swelling of the scrotum

Table 3: Treosulfan Side Effects in Children		
Very Common (10% or Greater)	**Common (1% - 9%)**	**Uncommon/rare/unknown frequency**
		Treatment-related secondary cancer
		Venoocclusive Disease/Sinusoidal obstruction syndrome (injury to the liver that can result in enlarged liver, liver pain, abdominal fluid and abnormal liver tests)

There have been isolated reports of seizure in infants (4 months of age or less) after receiving treosulfan combined with fludarabine as in this study. Very young children will be closely watched for signs of neurologic side effects.

Table 4: Treosulfan Side Effects in Adults			
Very Common (10% or Greater)	**Common (1% - 9%)**	**Uncommon (0.1% - 0.9%)**	**Rare/unknown frequency**
Abnormal liver tests	Abdominal/ esophageal pain	Abdominal bloating	Abnormal enzyme test – increased lactate dehydrogenase (LDH)
Anemia (low red blood cell count which can lead to fatigue)	Abnormal heartbeat	Bruising (small red or purple spots on the skin caused by bleeding into the skin)	Abnormal kidney function test
Diarrhea	Back pain	Chest pain	Acidosis (more acid than normal in the blood)
Feeling weak or tired	Bone, joint, or muscle pain	Confusion	Allergic reaction at the site of the drug injection
Fever	Chills	Death of skin tissue	Anal inflammation
Hair loss	Constipation	Dry mouth	Blood clot
Infections (bacterial, viral, fungal)	Decreased appetite	Dry skin	Burning or prickling sensation on the skin
Low platelet counts which increases the risk of bleeding	Difficulty swallowing	Excess fluid in the body cavity that surrounds the lungs	Cardiac arrest
Low white blood cell count which increases the risk of infection	Dizziness (feeling faint, woozy, weak or unsteady)	Glucose intolerance (high or low blood sugar)	Cough
Mucositis/stomatitis (painful inflammation/sores of the lips and/or lining of	Hand-foot syndrome (redness, swelling, and pain on the palms of the hands and/or soles of the feet)	Hiccups	Darkening of the skin

Table 4: Treosulfan Side Effects in Adults			
Very Common (10% or Greater)	**Common (1% - 9%)**	**Uncommon (0.1% - 0.9%)**	**Rare/unknown frequency**
the mouth that may cause difficulties eating)			
Nausea	Headache	Hyperhidrosis (excessive sweating)	Difficulty speaking
Vomiting (throwing up)	Hematuria (blood in urine)	Liver failure	Dry eyes
	High blood pressure	Lung infection including pneumonia that may require mechanical ventilation	Dysphonia (vocal changes)
	Hypersensitivity (overactive immune system which can range from mild to severe)	Mouth hemorrhage (excessive bleeding from the mouth)	Enlarged liver
	Indigestion	Numbness or pain in hands and feet	Encephalopathy (brain disease that can include temporary or permanent damage)
	Insomnia (trouble sleeping)	Pain	Fainting
	Itching	Pain with urination / urinary tract pain	Feeling cold
	Low blood pressure	Pulmonary Hemorrhage (bleeding within the lungs)	Gastric or intestinal bleeding which can be severe
	Mouth pain	Severe brain bleeding	Heart attack
	Nosebleeds	Severe skin rash with sores and/or peeling of skin	Heart failure
	Pain in extremities	Throat, lung, or mouth inflammation	Hepatotoxicity – damage to the liver including abnormal liver tests (not related to venoocclusive disease / sinusoidal obstruction syndrome)

Table 4: Treosulfan Side Effects in Adults			
Very Common (10% or Greater)	**Common (1% - 9%)**	**Uncommon (0.1% - 0.9%)**	**Rare/unknown frequency**
	Rash	Throat pain	Hypoxia (decrease in the amount of oxygen reaching the tissues)
	Redness of skin	Treatment-related secondary cancer	Inflammation of the bladder
	Sepsis, septic shock (overwhelming blood infection, can be fatal)	Venoocclusive disease / Sinusoidal obstruction syndrome (injury to the liver that can result in enlarged liver, liver pain, abdominal fluid and abnormal liver tests)	Liver pain
	Severe loss of kidney function which may require artificial kidney machine	Vertigo (spinning feeling)	Muscle weakness
	Stomach inflammation		Restlessness or jerking
	Sudden reddening of the face and/or neck		Severe bleeding
	Swelling		Severe inflammation of the colon
	Trouble breathing		Swelling around the heart
	Weight loss or gain		

Table 5: Fludarabine Side Effects		
Likely (May happen in more than 20% of patients)	**Less Likely**	**Rare, but Serious** (May happen in 2% or fewer patients)

	(May happen in 20% or fewer patients, but more than 2%)	
• Cough • Feeling tired or irritable • Infection, especially when white blood cell count is low • Low number of cells that help your blood clot • Low number of red blood cells, which may cause tiredness • Pain	• Chills • Confusion • Damage to brain, lungs or other organs • Diarrhea • Numbness and tingling in arms and legs • Nausea, vomiting, loss of appetite • Mouth sores, which can make it hard to swallow	• Blood in urine • Changes in vision • Coma • Kidney damage, which may require an artificial kidney machine • Liver damage • Seizures

Table 6: rabbit anti-thymocyte globulin (rATG) Side Effects		
Likely	**Less Likely**	**Rare, but Serious**

(May happen in more than 20% of patients)	(May happen in 20% or fewer patients, but more than 2%)	(May happen in 2% or fewer patients)
• Fast heart rate • Headache • High blood pressure • High or low potassium levels in the blood • Infection, which may cause fever and chills • Low number of red blood cells, which may cause tiredness • Low number of white blood cells, which may cause infections • Low number of cells that help your blood clot • Nausea, vomiting, diarrhea, constipation, stomach pain • Pain, including joint and muscle pain	• Abnormal blood test results, including high fat or mineral levels in the blood • Anxiety • A type of lymphoma called post-transplant lymphoproliferative disease (PTLD) • Cough • Tiredness • Rash, excessive itching • Reaction to the infusion, which may cause itching, fever, chills, low blood pressure and problems breathing • Excessive sweating • Swelling of the body • Problems sleeping	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swollen face or throat

Table 7: Methotrexate Side Effects		
Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Higher risk of sunburn or rash • Nausea, vomiting, loss of appetite • Mouth sores, which can make it hard to swallow	• Blood clot, which may cause swelling, pain, shortness of breath • Bruising, bleeding • Diarrhea, sores in the gastrointestinal tract • Hair loss • Infections • Kidney damage • Liver damage, which may cause yellowing of eyes and skin, generalized swelling • Low number of red blood cells, which can cause tiredness • Too much fluid around heart	• Cancer • Bleeding in your belly which may cause stomach pain, black tarry stool, or bloody vomit • Lung damage, which may cause shortness of breath, confusion • Severe skin rash with blisters and peeling which can also affect the mouth and other parts of the body

Table 8: Tacrolimus Side Effects		
Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Abnormal levels of sugar, fat, and electrolytes in the blood • Constipation, diarrhea, nausea, vomiting, reflux, low appetite • Difficulty sleeping • Dizziness • Feeling of "pins and needles" in arms and legs • Headache	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swollen face or throat • A tear or a hole in the bowels which may cause belly pain or require surgery • Brain damage, which may cause headache, seizure, blindness • Cancer	• Damage to small blood vessels, which can cause small blood clots and organ damage

Table 8: Tacrolimus Side Effects		
Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• High blood pressure which may cause dizziness, chest pain • Itching, rash • Kidney damage which may cause swelling, may require an artificial kidney machine • Low number of blood cells to clot, which may cause bruising or bleeding • Liver damage • Low number of red blood cells, which may cause tiredness • Low number of white blood cells, which can cause infection • Swelling of the body • Tremors	• Change in the heart rhythm, abnormal heartbeat or heart stops beating • Heart attack or failure which may cause chest pain, swollen ankles and tiredness • Lung damage, which may cause shortness of breath	

It is very important that you **do not eat grapefruit or drink grapefruit juice** while taking tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study. Common soft drinks that have bergamottin are *Fresca, Squirt, Sundrop* and *Sunny Delight*.

Potential Risks and Side Effects of the BMT

There are many potential risks of having a bone marrow transplant as listed below regardless of enrollment on this research study.

- **Damage to the organs in your body.** This could affect any organ in your body such as your heart, lungs, liver, gut, kidneys, bladder and brain. Although many patients recover, these complications may result in organ failure, permanent damage or even death.
- **Serious infections.** It can take your immune system many months to recover from BMT. During this time, you have a higher risk of infections. You will take medicines to lower your

risk, however these don't always work. If you have an infection, you may have to stay in the hospital. Although most infections can be treated, some may cause death.

- **Disease comes back.** Your disease may not go away with BMT, or it may come back even if the BMT works at first.
- **Graft failure.** The blood-forming cells from your donor (the "graft") may not grow inside your body. The risk of this happening is up to 15%. Graft failure may cause low blood counts for a long time. If this happens, you may need another BMT. Graft failure can cause death.
- **Cancer.** You could develop a blood cancer, such as myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or other cancers. If this happens, it's usually 2-10 years after BMT but can develop any time after BMT. We don't know the risk of developing cancer after treatment with treosulfan. With other chemotherapy drugs that have been used for BMT the risk is less than 10%. If cancer develops, you may need more treatment with chemotherapy or another BMT. Some patients have developed cytogenetic abnormalities (abnormal chromosomes) in bone marrow cells following transplant that may be a result of the chemotherapy medicines. The long-term risks are not completely understood. One potential risk is the development of MDS or a leukemia.
- **Damage to your thyroid or other endocrine glands.** This can affect the thyroid function and patients may require medication. In addition, in children this can affect growth and delay puberty which also may require medication.
- **Serious bleeding.** Your red blood cells, white blood cells, and platelets can be slow to recover after BMT. This means you'll be at risk for bleeding and infections. Until your blood counts recover, you'll need blood and platelet transfusions and antibiotics to prevent infections from occurring.
- **Non-physical risks.** Patients who have a BMT may experience non-physical risks including that you may not be able to attend school or work.
- **Risks of blood draws.** There are no major risks with blood draws. A blood draw can hurt a little and may cause a bruise. On rare occasions, people feel lightheaded or faint. Only trained people will draw your blood.
- **Graft-versus-host disease (GVHD).** GVHD happens when the donated cells see your body as foreign and attack it. GVHD can be treated, but treatment can take months to years. Sometimes GVHD is severe and may lead to death. You'll be watched closely for this complication and given drugs to prevent and/or treat it. GVHD is treated with drugs that weaken the immune system so you may be more likely to get serious infections while you're taking them. GVHD can develop in the early weeks or months after BMT. This is often called acute GVHD. GVHD can also develop months or years after BMT. This is often called chronic GVHD.

Acute GVHD symptoms:

- Skin rash, discoloration, and/or tightness of skin
- Lack of appetite, stomach cramps or abdominal pain, nausea, vomiting, diarrhea or "full" feeling in stomach, weight loss
- Liver problems, which can make the skin yellow

Chronic GVHD symptoms:

- Dry eyes, problems with vision
- Hair loss
- Liver problems
- Mouth problems, including dry mouth, mouth sores, dry and sore lips or throat, problems swallowing
- Skin rash or thickening (scleroderma)
- Difficulty moving joints
- Shortness of breath
- Muscle cramps, pain or weakness

Other Treatments or Medicines

Some medicines react with each other, so it's important to tell the study doctor or staff about any other drugs, treatments, or medicines you're taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments. It's also important that you tell the study staff about any changes to your medicines while you're in the study.

Reproductive Risks/Potential Risks to the unborn child

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.

It is important that both women who can become pregnant and their male partners use birth control for at least 1 year after transplant while on this study.

- **If you are female:**

If you 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 through 12 months post-transplant or off GVHD prevention (tacrolimus), whichever is later. during your transplant and continue until you are finished with

your GVHD prevention treatment. You may want to talk with your doctor about potential ovary banking before having a transplant.

Effective birth control is defined as the following:

1. Not having any vaginal sex (abstinence)
2. Consistently using birth control pills or patch
3. Use of an injectable birth control (for example, Depo-Provera or Norplant)
4. Having tubal sterilization (tied tubes)
5. Having placement of an IUD (intrauterine device)
6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have vaginal sex.

Tell your doctor right away if you become pregnant during the study. Your doctor will discuss the risks to your unborn child and options with you.

- **If you are male:**

Your body may not be able to produce sperm (become sterile). You should talk with your doctor about potentially banking your sperm before having a transplant. Please check with your doctor to understand more about these risks.

You must use one of the following birth control methods:

1. Not have any vaginal sex (abstinence)
2. Vasectomy or female partner who had a tubal ligation (tied tubes)
3. Use of condoms with contraceptive foam every time you have sex.

Or your partner must:

1. Consistently use birth control pills or patch
2. Use injectable birth control (for example, Depo-Provera or Norplant)
3. Have placement of an IUD (intrauterine device)
4. Use diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have vaginal sex.

Tell your doctor right away if your partner becomes pregnant during the study. Your doctor will discuss the risks to your unborn child and your options.

Unforeseen Risks

Other new risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. There may be some unknown or unanticipated side effects from this treatment. The study team will do everything they can to keep you safe and lower your risk of side effects.

For more information about risks and side effects, ask your study doctor.

5. Your Rights to Withdraw, Ask Questions, and Seek Other Treatment

Being in this study is your choice. You can choose **not** to be in this study or leave this study at any time. If you choose to not join or leave this study, it won't affect your regular medical care in any way. If at any time you are considering leaving the study, talk to your study doctor about your health and safety.

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

Dr. Lauri Burroughs (206) 667-7385
Research Coordinators: (206) 667-7385 or (206) 667-4916 or pager (206)314-1739

If you want to talk with someone not directly involved in the study, or have any complaints or questions about your rights as a research participant, you may contact:

NMDP Institutional Review Board Administrator at: 1 (800) 526-7809
Director of Institutional Review Office, Fred Hutchinson Cancer Center at:
(206) 667-5900 or irodirector@fredhutch.org
Human Subjects Division University of Washington at: (206) 543-0098

You must tell Lauri Burroughs, MD if you decide to leave the study.

If you choose not to join, other options are available. Your study doctor will talk with you about your options. If you decide not to join this study, your medical care will not be affected in any way. If you join this study, you may not be able to be in other clinical trials at the same time. Your study doctor can answer questions you may have about other clinical trials.

Your other choices may include:

- A BMT using different medicines to prepare your body for BMT
- Joining another clinical trial, if available (check with your doctor)
- Treatment of bone marrow failure symptoms
- No treatment

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

6. New Information Available During the Study

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

7. Privacy, Confidentiality, and Use of Information

Your privacy is very important to us. The study doctors, study sponsors, and other groups with access to your study-related medical information will do everything they can to protect it. This study has a "Certificate of Confidentiality," which means the study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be shared if required by law. If this happens, the study doctors will do their best to make sure that any information that goes out to others will **not** identify you.

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 confidential (private). However, we cannot promise total privacy.

To make sure the study is running ethically, some government agencies or other groups may need to access part of your medical records. For this study, those groups include:

- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the NMDP registry and The Emmes Company, who are coordinating the studies of the BMT CTN
- The Food and Drug Administration (FDA) and National Institutes of Health (NIH), which includes the National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Office of Human Research Protection (OHRP)
- Data and Safety Monitoring Board (DSMB), not part of the study site
- Fred Hutchinson Cancer Center, University of Washington Medical Center, Seattle Children's Hospital
- Institutional Review Boards (IRBs) responsible for reviewing this study
- Medac GmbH, the drug company that makes treosulfan and provides it for this study
- Fred Hutchinson Cancer Center, the regulatory sponsor that holds the IND for the study along with the regulatory sponsor's medical monitor for this study.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Study information may also be used for research in the future. These projects could be related to your disease or similar diseases, or development of the study drug.

We might use information from this study to get approval from the government, like the Food and Drug Administration (FDA).

For the treosulfan research study, private information, blood, or tissue taken during the study may be used for future research. If the study team does this, the information, blood, or tissue will not be attached to you or your name in any way and results of the research done with it will not be given to you.

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

Data about your health, including follow up after 1 year may be obtained by the BMT CTN from the CIBMTR, which captures information on all US transplants.

8. Leaving the Study

You can choose to leave the study at any time.

You may also be told to leave the study for reasons such as:

- You don't 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're having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

Even if you leave the study, the information already collected from you will be included in the study evaluation.

9. Cost and Reimbursement

You will **not** be paid for joining this study. You will not be paid or reimbursed for any extra expenses (such as travel or meals) from your participation in this study.

The study drug, treosulfan, is being provided at no cost to you by the drug company, Medac. The visits for this study are standard medical care for patients with bone marrow failure disorders and will be billed to your health insurance company. You and/or your health insurance company will need to pay for all the costs of standard medical treatment in this study.

Some health insurance plans will not pay for costs of care when you take part in a research study. Check with your health plan or insurance company to find out if they will pay.

A new drug or product may be developed from this study. The study site will **not** pay you if a commercial product is developed from blood or tissue taken from you during this study.

For questions about your costs, financial responsibilities, and/or health insurance coverage for this study, please contact Fred Hutchinson Cancer Center Patient Financial Services at (206) 606-1113.

Physical Injury as a Result of Participation

Tell your study doctor or staff if you think you've been hurt because of being in this study. You'll get medical treatment if you're hurt as a result of this study. You and/or your health insurance company will be charged for this treatment.

Medac, the provider of the study drug, will pay the costs of medical treatment for injuries resulting directly from a defect in the design or manufacture of the study drug.

In case of injury resulting from this study, you don't lose any of your legal rights to seek payment by signing this form.

10. Health Insurance Portability and Accountability Act 1 (HIPAA) Authorization to use health information for research

Your local study site will give you a separate form with information about the Health Insurance Portability and Accountability Act 1 (HIPAA).

11. Additional Optional Research Studies

Overview

If you join one of these studies, you may:

1. Have extra blood samples collected before and after you receive treosulfan
2. Have extra blood or bone marrow samples collected to use to grow cells
3. Take surveys about your quality of life

Purpose

We are doing these studies to:

1. Learn how the drug treosulfan is processed in the body
2. Improve diagnosis and treatment for patients with bone marrow failure
3. Learn how people feel and how well they can do everyday activities after this treatment

What will happen

You can participate in 1 or more of these 4 optional research studies:

1. Treosulfan Pharmacokinetics (PK) Research Study

We will collect blood samples from you before and after you receive treosulfan. A total of 12 blood samples (6 samples per day) will be collected over the first 2 days of treosulfan administration (referred to as day -6 and day -5 before BMT). The research samples will be collected at the following times:

- Before you receive the treosulfan
- At the end of the treosulfan infusion
- Twenty minutes after the end of the treosulfan infusion
- Three and a half hours after the start of the treosulfan infusion
- Six hours after the start of the treosulfan infusion
- Nine hours after the start of the treosulfan infusion

About 1.5-2 teaspoons of blood will be drawn for PK testing each day.

We will perform Treosulfan PK studies in approximately 5 patients for each of the following age groups:

1) 1 year to < 2 years,
2) 2 years to <4 years,
3) 4 years to <12 years and
4) ≥ 12 years (total patients approximately 20).

If your age group has reached the maximum number of participants, this optional study may no

longer be available to you.

These samples are strictly for research purposes to learn about treosulfan. We won't adjust the treosulfan dose based on the results of these tests. It is optional to participate in these blood draws, which means that even if you decide to be treated in this study, you may decide not to have these additional blood draws.

2. Biological Research Study

The goal of this study is to improve diagnosis and develop better treatments for patients with bone marrow failure conditions. We will collect clinical information from your medical record as well as samples of blood and bone marrow at the same time these samples are already being taken. Clinical information will include diagnosis, physical examination, lab results, and pathology reports. From the collected tissue samples, we can study cells, DNA (genetics), RNA and proteins from patients, to learn what causes bone marrow failure and how better to diagnose and treat these conditions. We will study genes that contribute to bone marrow failure and its complications. If you provide samples and do not continue to transplant your samples will be stored for research.

Note: All extra samples of blood or marrow, are obtained for research when they are being drawn for your clinical care. No extra procedures or needle pokes are performed to obtain these research samples. For this study, we are asking you to donate about 2 teaspoons of blood and about 2 teaspoons of bone marrow if you have a bone marrow procedure prior to the transplant and around 1 year after the transplant.

The blood or marrow collected in this research may be used to create a "cell line" that can be grown in the laboratory. A cell line can continue to grow and make more cells indefinitely. This allows researchers to have an unlimited supply of your cells in the future without asking for more samples from you. The researchers will use these cells to try to learn more about bone marrow failure.

We may use cells taken from your blood or marrow to create a type of cell known as a pluripotent stem cell. Stem cells can be used to create other types of cells and tissue, such as blood cells. Your cells might be used to study genetic changes. The researchers will use your cells to try to learn more about bone marrow failure.

3. Quality of Life Survey Study

The researchers want to understand how transplant using treosulfan-based conditioning affects quality of life (QoL).

If you agree to complete the optional QoL surveys, you will receive a survey:

- Before BMT
- About 6 months after BMT
- 1 year after the BMT

The survey will ask you a series of questions about how healthy you feel and how well you can do your everyday activities. Your doctor and/or the research team will give you instructions and materials to complete each survey. These questions can be answered either via an online survey or a paper survey mailed or given to you. The CIBMTR will collect the survey data and will reach out to you if surveys are not completed to ensure you received the online link or paper survey and answer any questions you have. Each survey will take 2-3 minutes to complete.

This information will be used for research purposes. You can skip any questions you want. You can also stop the survey at any time.

This survey is only available if you speak English or Spanish.

Benefits

Being in this research may not help you right now. The information from these studies may help doctors learn more about how to treat bone marrow failure disorders better. This could help people with bone marrow failure disorders in the future.

Risks

Your confidentiality (privacy) could be lost. We will use safety measures with your blood and/or bone marrow samples and your information to make sure that it is kept private. The chance that your information will be given to someone else is very small.

There are no major risks with blood draws. A blood draw can hurt a little and may cause a bruise. On rare occasions, people feel lightheaded or faint. Only trained people will draw your blood.

Also, some of the survey questions or topics may upset you. If this happens, your doctor can connect you with a counselor or trained support specialist, if needed.

Your doctor will not be able to see your answers on the surveys. The answers will not be shared with anyone until after the study is done and you will not be able to be identified. There is a

small risk that a person who shouldn't be able to see your survey could find out which answers are yours. The study team and the CIBMTR will do everything it can to keep your answers confidential.

For more information about risks and side effects, ask your study doctor.

Privacy, Confidentiality and Use of Information
Certain information may be shared with you depending on which studies you agree to participate.

For the biological study, clinical information, blood, or marrow taken during the study may be used for future research. The information, blood, or marrow will be coded to protect confidentiality.

For the QoL surveys, we'll do our best to make sure that your medical and personal information in your study record is kept private. However, we can't promise total privacy. Your personal information will only be labeled with a number code. No information that would let others know who you are or that you were in the study will be published or presented at scientific meetings.

We'll only share your medical and personal information if you request it in writing or agree in writing to share it, or if we are required by law. A possible risk is the loss of confidentiality about your medical information. We will do our best to make sure that your personal information is kept private. The chance that this information will be given to someone else is very small.

Use of your blood samples for future research

The blood samples will be sent to the Fred Hutchinson Cancer Center Pharmacokinetics Lab (Treosulfan PK Research Study) or TransLab at Boston Children's Hospital (Biological Research Study for processing and storage. The research sample will be given a bar code that **cannot** be linked to you.

- Doctors and researchers may use the stored blood samples for BMT CTN research. In the future, other researchers can use the unused blood samples and data. They will need to apply to study the blood samples. The BMT CTN Steering Committee and/or Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the researchers are qualified and that the research is high quality.

- Genetic information from your stored blood sample might be used in **genome-wide association (GWA) studies** for future research done or supported by the National Institutes of Health (NIH). GWA studies help scientists find genes involved in disease or treatment. Each study can look at thousands of genetic changes at one time.

- If your sample is used in a GWA study, the researcher is required to add your test results and information into a shared, public research database. The database 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.

- A federal law called the **Genetic Information Nondiscrimination Act (GINA)** makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information and may not use your genetic information when making decisions about your health insurance. This federal law will **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Leaving the Study

You may be told to leave the study if you are not able to complete the study tests, such as blood draws or surveys.

Cost

Your extra blood or bone marrow samples will be used only for future research and will not be sold. A new drug or product may be developed from the research done with your blood samples. You will not get paid for any samples or for any products that may be developed from current or future research. You will not get paid for participating in the QoL surveys. You will not be charged for taking part in this study.

TITLE: BMT CTN 1904: Hematopoietic Cell Transplantation Using Treosulfan-Based Conditioning for the Treatment of Bone Marrow Failure Diseases

- I have read and understood this Consent Form. The purpose and description 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 have had the chance to discuss my participation in this research study with a family member or friend if I choose.
- I understand that…
    - I may not directly benefit from taking part in the study.
    - My name and personal information will not be identified even if information gained during the study is published.
    - 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 will be given a copy of this signed consent form.
    - I do not give up any legal rights by signing this form.

Optional Research Studies:

Treosulfan PK Research Study

☐ Not Applicable - accrual for patient age group has been met (to be marked only by the person obtaining consent, if appropriate).

☐ I agree to give blood samples for the treosulfan research study.

☐ I do **not** agree to give blood samples for the treosulfan research study.

Biological Research Study

☐ I agree to give blood samples or marrow samples (if a bone marrow is being done for clinical purposes) for the biological research studies.

☐ I do **not** agree to give blood samples or marrow samples (if a bone marrow is being done for clinical purposes) for the biological research studies.

Quality of Life Survey Study

☐ I agree to participate in the quality of life surveys (both the parent and patient questionnaires if applicable).

☐ I do **not** agree to participate in the quality of life surveys (both the parent and patient questionnaires if applicable).

_____ _____

Participant Name (or Parent/Guardian) Date (MM/DD/YYYY)

_____

Participant Signature (or Parent/Guardian)

Physician certification

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 (MM/DD/YYYY)

_____

Signature of Counseling Physician

Interpreter certification (if needed)

I certify that I have provided an accurate interpretation of this consent form. I believe the participant has understood the information provided.

_____ _____

Interpreter Name Date (MM/DD/YYYY)

_____

Interpreter Signature