

BMT CTN 1301, v3.0

A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

Your Name: _____

Study Title: A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

Protocol: BMT CTN # 1301, version 3.0

Principal Investigator: *[Insert local PI name]*

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 compare 3 types of treatment to see which one is best at preventing **chronic Graft-versus-Host Disease (GVHD)**. You are being asked to join this study because:

- You have a disease that can be treated by an **allogeneic stem cell transplant** (using bone marrow or peripheral blood stem cells (PBSCs) from a donor) and
- Your doctor plans to use a **standard intensity conditioning regimen** for your transplant.

See **Section 2: Study Background** for a definition of the bolded terms.

Your study participation will last for **2 years after your transplant**. This study will take at least 2 years total and will include 345 participants. There will be 115 participants in each of the treatment groups.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

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 do not 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 choices if you do not 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 and the NIH will make decisions about how to manage the study.

The Miltenyi Biotec company is supporting this study with supplies and money. This company makes a tool that helps prepare the donated stem cells before giving them to patients.

An allogeneic stem cell transplant (allogeneic transplant) is a standard treatment for blood cancers like acute leukemia and myelodysplastic disorder. An allogeneic transplant replaces your abnormal (or diseased) blood cells with blood cells from a donor. It requires a close tissue match between you and the donor. Your donor could be a family member, like a sister or brother, or it could be an unrelated person.

An allogeneic transplant first uses chemotherapy and possibly radiation to destroy the abnormal blood cells or stop them from growing. Then, we replace the destroyed cells with the new cells from your donor.

The chemotherapy and radiation you get to destroy the abnormal cells and prepare your body for transplant is called the **conditioning regimen**.

A common problem after allogeneic transplant is a condition called Graft Versus Host Disease (GVHD). “Graft” is the donor blood cells that you will get during your transplant. “Host” is the person (in this case, you) who gets the donated cells.

GVHD is a side effect where the donor cells (or graft) attack and damage some of your tissue. There are 2 kinds of GVHD: acute and chronic. Acute GVHD usually develops within the first 3 months after transplant. Chronic GVHD usually develops later and lasts longer.

GVHD can cause:

- Skin rash
- Stomach (or intestinal) problems like nausea (feeling sick to your stomach), vomiting (throwing up), or diarrhea (loose stool)
- Damage to your liver
- Hepatitis or jaundice (yellowing of the skin)
- Increased risk of infection

Chronic GVHD can affect many organs and greatly impact your quality of life.

(See **Section 6: Risks and Discomforts** for more information on the side effects of GVHD, and GVHD prevention drugs.)

3. Study Purpose

We are inviting you to take part in this study because you have acute leukemia or myelodysplasia, and an allogeneic transplant is a treatment option. We are doing this research to compare 3 different treatment

combinations to see if 1 or more is better than the standard treatment for preventing **chronic GVHD**. The treatments are listed below (**Table 1**):

Table 1: Treatment Groups

Group A:	CD34 Selected Peripheral Blood Stem Cells (new treatment)
Group B:	Bone Marrow Transplant followed by Post-Transplant Cyclophosphamide (new treatment)
Group C:	Bone Marrow Transplant with Tacrolimus and Methotrexate as GVHD Prevention (standard treatment)

Doctors are mostly interested in learning how Groups A and B compare to Group C. The study will help doctors decide which treatment is best at preventing chronic GVHD. We also want to learn how much

GVHD is affecting your quality of life, if at all.

(See **Section 5: Study Tests and Treatments** for more information on the treatment groups.)

4. Rights to Ask Questions and/or Withdraw

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

[insert contact info]

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 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 that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, during your treatment, and for **2 years** after transplant. All patients in this study need to have a matched donor.

Before You Start Your Treatment

Before you begin, you will need to have several exams (tests) and checkups to find out if you can be in the study. These exams and checkups are part of regular cancer care. They would be done even if you don't join the study. The exams include:

- Medical history
- Physical exam, including height and weight
- Blood and urine tests
- Heart function tests, including EKG and ejection fraction
- Lung (pulmonary) function tests
- Tests to see how much cancer is in your body (cancer re-staging). This might include a bone marrow aspirate or biopsy. This is where samples of your bone marrow are taken from your hip bone with a large needle.
- Chest X-ray or chest CT
- A pregnancy test if you are a woman and able to have children. If you are pregnant, you will not be able to take part in this study.

- Health quality of life surveys

We will also talk with you about providing extra blood samples for future research (see **Section 17: Blood Samples for Future Research**). This is completely optional.

The quality of life surveys are for study participants who are:

- Children and teenagers, 8 – 18 years old, who speak English, and
- Adults, 18 or older, who speak English or Spanish

The survey will ask about:

- Any side effects of your treatment
- Any health problems
- How well you can do things that are important to you
- How you relate to other people
- Your feelings.

We will ask you to fill out paper surveys at the clinic or hospital. The surveys will take less than 30 minutes to finish. If you need to take the survey by phone, an interviewer will contact you before your transplant. You may skip any questions you wish.

Randomization

We will use a computer to randomly assign you to 1 of 3 treatment groups (A, B, or C). You will have an equal chance of being

placed in 1 of the 3 groups. You, your doctor, and the study researcher won't have any control over which treatment group you're assigned.

During Your Treatment

The tables below describe the 3 treatment groups that will be used in this study. Each treatment includes a conditioning regimen (chemotherapy and/or radiation), allogeneic transplant, and GVHD prevention. Your doctor will decide on the conditioning

regimen. You will be given the chemotherapy drugs by mouth or by IV (through your vein). The amount of chemotherapy drugs you receive will be based on your weight. The chemotherapy and radiation may cause side effects. Some of these side effects may be life-threatening (see **Section 6: Risks and Discomforts**).

Some of the treatment groups include a medicine called Mesna. Mesna helps prevent bladder discomfort and hemorrhaging (bleeding).

Group A: CD34 Selected Peripheral Blood Stem Cells		
Your doctor will choose 1 of 2 conditioning regimens <u>before transplant</u> :	Graft (source of donor cells) for <u>transplant</u> :	GVHD prevention treatment:
<p>1. Total Body Irradiation (TBI), Chemotherapy drugs (3), and Mesna:</p> <ul style="list-style-type: none"> • TBI, given 3 times a day for 4 days (11 doses total), starting 9 days before transplant • Thiotepa, given once daily for 2 days, starting 5 days before transplant • Anti-Thymocyte Globulin (rATG), given over 6-8 hours, once daily for 2 days, starting 4 days before transplant • Cyclophosphamide (Cy), given once daily for 2 days, starting 3 days before transplant • Mesna – your doctor will decide how many doses based on Cy dose 	Peripheral blood stem cells	The donor cells will be put through a device, CliniMACS, that removes the immune cells responsible for causing GVHD.

<p>2. Chemotherapy drugs (4):</p> <ul style="list-style-type: none">• Busulfan, given over 2 hours, 4 times each day for 3 days, starting 9 days before transplant• Melphalan, given over 30 minutes, once daily for 2 days, starting 6 days before transplant• Fludarabine, given over 30 minutes, 5 times a day for 5 days, starting 6 days before transplant• Anti-Thymocyte Globulin (rATG), given once daily for 2 days, starting 3 days before transplant		
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<p>Group B: Post-Transplant Cyclophosphamide (Cy)</p> <p>We'll give you medicines to kill the donor cells that are attacking your body after your transplant.</p>		
<p>Your doctor will choose 1 of 3 conditioning regimens <u>before transplant</u>:</p>	<p>Graft source for <u>transplant</u>:</p>	<p>GVHD prevention drugs:</p>
<p>1. Chemotherapy drugs (Busulfan and Cy) and Mesna:</p> <ul style="list-style-type: none"> • Busulfan, given for 4 days. Your doctor will decide when you will start taking this drug and how many doses you will get every day. • Cyclophosphamide (Cy), given once daily for 2 days, starting 3 days before transplant • Mesna – your doctor will decide when you will start taking this drug and how many doses you will get every day. 	<p>Bone marrow</p>	<p>Cyclophosphamide will be given by IV (through your vein), over 1-2 hours, on Days 3 and 4 after your transplant.</p>
<p>2. Chemotherapy drugs (Busulfan and Fludarabine):</p> <ul style="list-style-type: none"> • Busulfan, given for 4 days. Your doctor will decide when you will start taking this drug and how many doses you will get every day. • Fludarabine, given 4 times a day for 4 days, starting 5 days before transplant. Each dose will take about 30 minutes. 		
<p>3. Total Body Irradiation (TBI) <u>and</u> Chemotherapy drugs (Cy):</p> <ul style="list-style-type: none"> • TBI – your doctor will decide how many doses, for 4 days, starting 7 days before transplant • Cyclophosphamide (Cy), given once daily for 2 days, starting 3 days before transplant • Mesna – your doctor will decide when you will start taking this drug and how many doses you will get every day. 		

<p>Group C: Tacrolimus and Methotrexate (standard treatment)</p> <p>We'll give you medicines to prevent the donor cells from attacking your body before your transplant.</p>		
<p>Your doctor will choose 1 of 4 conditioning regimens <u>before transplant</u>:</p>	<p>Graft source for <u>transplant</u>:</p>	<p>GVHD prevention drugs:</p>
<p>1. Chemotherapy drugs (Busulfan and Cy) and Mesna</p> <p>a. Busulfan, your doctor will decide when you will start taking this drug and how many doses you will get every day.</p> <ul style="list-style-type: none"> ▪ Cyclophosphamide (Cy), given over 1-2 hours, once daily for 2 days, starting 3 days before transplant ▪ Mesna – your doctor will decide when you will start taking this drug and how many doses you will get every day. 	<p>Bone marrow</p>	<p><u>Before your transplant</u>:</p> <p>Tacrolimus will be given as a pill by mouth or by IV (through your vein) 2 times every day, starting 3 days before transplant. The amount will slowly be lowered and eventually stopped. This process will take place over several months.</p> <p><u>After your transplant</u>:</p> <p>Methotrexate will be given by IV (through your vein) on Days 1, 3, 6 and 11 after your transplant.</p>
<p>2. Chemotherapy drugs (Busulfan and Fludarabine):</p> <p>a. Busulfan, your doctor will decide when you will start taking this drug and how many doses you will get every day.</p> <p>b. Fludarabine, given 4 times a day for 4 days, starting 5 days before transplant. Each dose will take about 30 minutes.</p>		
<p>3. Total Body Irradiation (TBI) <u>and</u> Chemotherapy drugs (Cy) <u>and</u> Mesna:</p> <p>a. TBI – your doctor will decide how many doses, for 4 days, starting 7 days before transplant</p> <ul style="list-style-type: none"> ▪ Cyclophosphamide (Cy), given once daily for 2 days, starting 3 days before transplant 		

<ul style="list-style-type: none"> ▪ Mesna – your doctor will decide when you will start taking this drug and how many doses you will get every day. 		
<p>4. Total Body Irradiation (TBI) and Chemotherapy drugs (Etoposide):</p> <ul style="list-style-type: none"> a. TBI – your doctor will decide how many doses, for 4 days, starting 7 days before transplant ▪ Etoposide, given one time, 3 days before transplant 		

Treatment Groups A and B don't require long-term use of GVHD prevention drugs. If you're assigned to Treatment Group A or B and you develop GVHD, your doctor will give you drugs to treat the GVHD. Your doctor will determine your treatment (drugs) and the amount based on your signs and symptoms.

Your Transplant (Peripheral blood stem cells (PBSCs) or bone marrow)

On your transplant day, we will give you the donated PBSCs or bone marrow through your catheter. It works just like a blood transfusion. The cells will travel to your bone marrow where they will start to make healthy, new blood cells after several weeks.

After Your Transplant

We'll evaluate (test) your health after your transplant. 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. You will be watched closely for any signs and symptoms of GVHD.

Health evaluations after transplant:

- 1) See **Table 1: Timeline of Exams After Your Transplant** for a schedule of when we will give you these exams.
- 2) Quality of life surveys (see **Before You Start Your Treatment** earlier in this section). We will ask you about your general health and how well you feel while you're in this study. Even though different treatments may treat a disease equally well, there might be differences in how patients feel or the side effects they have after their treatment. This is important information for when we evaluate the treatments in this study. You will take the surveys at the clinic or hospital on Days 100, 180, 365 and 730.
- 3) Optional blood samples for future research (see **Section 17: Blood Samples for Future Research**).

Table 1: Timeline of Exams After Your Transplant

Exams	Day <u>After</u> Transplant						
	Weekly until Day 63	100	150	180	270	365	730
Tests for toxicities, and infections	✓	✓	✓	✓	✓	✓	✓
Monitoring for CMV, EBV	✓	(Weekly until Day 100) ✓	✓	✓			
Tests for GVHD	✓	✓	✓	✓	✓	✓	✓
Blood tests for cell counts, liver and kidney function	✓	✓		✓		✓	✓
Tests to see how much cancer you still have		✓		✓		✓	✓
Quality of life surveys		✓		✓		✓	✓
Optional blood samples for research (if you consent)	(Day 35 only) ✓	✓		✓		✓	

6. Risks and Discomforts

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

The risks and discomforts of allogeneic transplant are the same if you join this study, or if you don't join this study. You might do better or worse with a standard transplant. Your healthcare team may give you medicines to help with side effects like

nausea (feeling sick to your stomach). In some cases, side effects can last a long time or may never go away.

Risks of Medications

The risks of the chemotherapy drugs, and/or radiation you get as part of the treatment are listed below. How often patients get each of side effects are shown in **Table 2**.

Table 2: Risks And Side Effects

Likely	What it means: This type of side effect is expected in <u>more than 20% of patients</u> . 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 in <u>20% of patients or fewer</u> . This means that 20 or fewer patients out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect is expected in <u>fewer than 2% of patients</u> . This means that 1 or 2 patients (or fewer) out of 100 might get this side effect. It doesn't happen very often, but is serious when it does.

Busulfan (Chemotherapy drug)

<p>Likely</p> <p>(May happen in more than 20% of patients)</p>	<p>Less Likely</p> <p>(May happen in fewer than 20% of patients)</p>	<p>Rare, but Serious</p> <p>(May happen in fewer than 2% of patients)</p>
<ul style="list-style-type: none"> ▪ Upset stomach or pain in the belly ▪ Constipation ▪ Diarrhea (loose stool) ▪ Feeling dizzy ▪ Water retention (storing extra water) ▪ Headache ▪ Heartburn ▪ Insomnia (not able to sleep) ▪ Loss of appetite ▪ Mouth sores (mucositis) ▪ Nausea (feeling sick to your stomach) ▪ Vomiting (throwing up) ▪ Runny nose ▪ Skin rashes ▪ Irregular or no menstrual periods in women ▪ Tachycardia (fast heart beat) 	<ul style="list-style-type: none"> ▪ Cough ▪ Hepatic Veno-occlusive disease (type of liver disease) ▪ High blood pressure ▪ High magnesium and phosphorus levels in the blood ▪ High sugar levels in the blood ▪ Infertility ▪ Low blood pressure ▪ Seizures ▪ Dyspnea (shortness of breath) 	<ul style="list-style-type: none"> ▪ Cataracts ▪ Lung fibrosis (scarring of lungs)

Cyclophosphamide (Cytoxan®) (Chemotherapy drug)

<p>Likely (May happen in more than 20% of patients)</p>	<p>Less Likely (May happen in less than 20% of patients)</p>	<p>Rare, but Serious (May happen in less than 2% of patients)</p>
<ul style="list-style-type: none"> ▪ Sores in mouth or on lips ▪ Loss of appetite ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Diarrhea (loose stool) ▪ Water retention ▪ Temporary hair loss ▪ Damage to male (testes) and female (ovaries) sex glands ▪ Infertility (inability to have children) ▪ Irregular or no menstrual periods in women ▪ Neutropenia (low white blood cell count and increased risk of infection) ▪ Thrombocytopenia (low platelet count and increased risk of bleeding) 	<ul style="list-style-type: none"> ▪ Bleeding in bladder ▪ Anemia (low red blood cell count) ▪ Damage to the fetus if you become pregnant while taking drug ▪ Stomach pain ▪ Skin rash 	<ul style="list-style-type: none"> ▪ Allergic reaction ▪ Scarring of lung tissue with cough and shortness of breath ▪ Serious skin rash ▪ Severe heart muscle injury and death (at very high doses) ▪ Second (new) cancers

If you are taking cyclophosphamide, your doctor may also prescribe you a medicine called **Mesna**. Mesna helps prevent bladder discomfort and bleeding that can occur from taking cyclophosphamide.

Etoposide (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in less than 20% of patients)	Rare, but Serious (May happen in less than 2% of patients)
<ul style="list-style-type: none"> ▪ Diarrhea ▪ Hair loss ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) 	<ul style="list-style-type: none"> ▪ Mouth sores (mucositis) ▪ Constipation ▪ Upset stomach or pain in the belly 	<ul style="list-style-type: none"> ▪ Allergic reaction ▪ Peripheral neuropathy (numbness and tingling in hands and/or feet)

Fludarabine (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in less than 20% of patients)	Rare, but Serious (May happen in less than 2% of patients)
<ul style="list-style-type: none"> ▪ Diarrhea (loose stool) ▪ Mouth sores ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Suppressed immune system (immune system not able to fight off) 	<ul style="list-style-type: none"> ▪ Fever ▪ Numbness and tingling in the hands and/or feet ▪ Feeling sleepy or tired ▪ Changes in vision ▪ Weakness 	<ul style="list-style-type: none"> ▪ Coma ▪ Cough ▪ Inflammation (swelling) of the lungs ▪ Interstitial Pneumonia (type of lung disease) ▪ Skin rash

infection as normal)		
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Melphalan (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in less than 20% of patients)	Rare, but Serious (May happen in less than 2% of patients)
<ul style="list-style-type: none"> ▪ Constipation ▪ Diarrhea(loose stool) ▪ Temporary hair loss ▪ Mouth sores (mucositis) ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) 	<ul style="list-style-type: none"> ▪ Abnormal heart beat ▪ Increased risk of Hepatitis ▪ Kidney failure 	<ul style="list-style-type: none"> ▪ Allergic reaction ▪ Interstitial Pneumonia (type of lung disease) ▪ Seizure ▪ Scarring of lung tissue

Total Body Irradiation (TBI)

<p>Likely</p> <p>(May happen in more than 20% of patients)</p>	<p>Less Likely</p> <p>(May happen in less than 20% of patients)</p>	<p>Rare, but Serious</p> <p>(May happen in less than 2% of patients)</p>
<ul style="list-style-type: none"> ▪ Diarrhea ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Stomach cramps ▪ Temporary hair loss ▪ Cataracts ▪ Stunted growth ▪ Low platelet count with increased risk of bleeding ▪ Low white blood cell count with increased risk of infection ▪ Pain and swelling of the parotid gland (salivary glands under the ears) ▪ Anemia ▪ Infertility (inability to have children) ▪ Endocrinopathies (such as thyroid disease or diabetes) 	<ul style="list-style-type: none"> ▪ Lung inflammation and pneumonia ▪ Redness of the skin ▪ Liver problems 	<ul style="list-style-type: none"> ▪ Second (new) cancers ▪ Difficulty swallowing ▪ Back problems ▪ Kidney problems

▪ Mouth sores (mucositis)		
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Thiotepa (Chemotherapy drug)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in less than 20% of patients)	Rare , but Serious (May happen in less than 2% of patients)
<ul style="list-style-type: none"> ▪ Low white blood cell count with increased risk of infection ▪ Diarrhea (loose stool) ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Liver damage ▪ Low sperm production in men ▪ Temporary hair loss ▪ Loss of appetite ▪ Missing or no menstrual period in women ▪ Mouth and throat sores ▪ Infertility (inability to have children) 	<ul style="list-style-type: none"> ▪ Liver abnormalities ▪ Skin rash ▪ Change in skin coloring ▪ Low platelet count with increased risk of bleeding 	<ul style="list-style-type: none"> ▪ Confusion ▪ Disorientation

Rabbit Anti-Thymocyte Globulin (rATG)

<p>Likely (May happen in more than 20% of patients)</p>	<p>Less Likely (May happen in less than 20% of patients)</p>	<p>Rare , but Serious (May happen in less than 2% of patients)</p>
<ul style="list-style-type: none"> ▪ Fever ▪ Shaking chills ▪ Low blood pressure ▪ Skin rash ▪ Itching ▪ Decreased platelet counts ▪ Decreased white blood cell counts 	<p>Serum sickness, consisting of :</p> <ul style="list-style-type: none"> ▪ Severe skin rashes ▪ Mouth sores ▪ Vaginal sores ▪ Pain/swelling of joints ▪ Kidney damage 	<p>Severe allergic reaction which may cause:</p> <ul style="list-style-type: none"> ▪ Life-threatening drop in blood pressure ▪ Wheezing ▪ Difficulty breathing ▪ Severe hives

Risks of Drugs Used to Prevent GVHD

If you’re assigned to Treatment Group C you will get medicines to help prevent GVHD after your transplant. The side

effects of the GVHD drugs usually stop when you’re done taking them.

Cyclosporine (Gengraf® or Neoral®) (GVHD prevention drug)

<p>Likely (May happen in more than 20% of patients)</p>	<p>Less Likely (May happen in less than 20% of patients)</p>	<p>Rare, but Serious (May happen in less than 2% of patients)</p>
<ul style="list-style-type: none"> ▪ Kidney problems ▪ Loss of magnesium, calcium, and potassium ▪ High blood pressure 	<ul style="list-style-type: none"> ▪ Liver problems ▪ Unwanted hair growth ▪ Growth of extra tissue on the gums (inside mouth) ▪ Burning, tingling or numbness in the hands, arms, feet or legs 	<ul style="list-style-type: none"> ▪ Seizures ▪ Changes in vision ▪ Formation of very small blood clots

Methotrexate (GVHD prevention drug)

<p>Likely</p> <p>(May happen in more than 20% of patients)</p>	<p>Less Likely</p> <p>(May happen in less than 20% of patients)</p>	<p>Rare</p> <p>(May happen in less than 2% of patients)</p>
<ul style="list-style-type: none"> ▪ Low white blood cell count with increased risk of infection ▪ Feeling tired ▪ Infections 	<ul style="list-style-type: none"> ▪ Nausea(feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Irritation or sores in the throat or mouth (mucositis) ▪ Diarrhea (loose stool) ▪ Upset stomach or pain in the belly ▪ Fever ▪ Chills ▪ Anemia (low red blood cell count) ▪ Abnormal liver tests ▪ Kidney failure 	<ul style="list-style-type: none"> ▪ Feeling dizzy ▪ Lung fibrosis (scarring of the lungs)

Tacrolimus (FK506, Prograf®) (GVHD prevention drug)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in less than 20% of patients)	Rare (May happen in less than 2% of patients)
<ul style="list-style-type: none"> ▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ High blood pressure ▪ Tremors (shaking) ▪ High cholesterol and triglyceride ▪ Low blood platelet count with increased risk of bleeding ▪ Infections 	<ul style="list-style-type: none"> ▪ Nausea (feeling sick to stomach) ▪ Vomiting (throwing up) ▪ Unwanted hair growth ▪ Liver problems ▪ Insomnia (not able to sleep) ▪ Foggy thinking ▪ Confusion 	<ul style="list-style-type: none"> ▪ Seizures ▪ Changes in vision ▪ Feeling dizzy ▪ Red blood cell damage

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*, and *Sunny Delight*.

Risks of Transplant

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

Graft-Versus-Host Disease (GVHD)

GVHD develops when the donor’s white blood cells attack your body. White blood cells are also called T cells. You are more likely to get GVHD if your donor’s tissue type does not closely match your tissue type. There are 2 kinds of GVHD: acute and chronic.

Acute GVHD

Acute GVHD usually develops within the first 3 months after transplant. You may experience these side effects with acute GVHD:

- Skin rash
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea
- Abdominal (stomach area) pain
- Problems with your liver (your doctor will run tests for this)
- Infection

Chronic GVHD

Chronic GVHD usually develops later and lasts longer. You may experience these side effects with chronic GVHD:

- Skin rashes
- Hair loss
- Thickened skin
- 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. Your doctor 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 involves taking a small piece of your skin to look at it under a microscope. 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 with drugs. In some cases, GVHD can be very hard to treat. It might also cause death.

Slow recovery of blood counts

The red blood cells, white blood cells, and platelets can be slow to recover after transplant. Until your blood counts recover, you will need blood and platelet transfusions. You'll be at risk for bleeding and infections. We might give you a drug called **Filgrastim** (G-CSF; Neupogen®) to speed up the recovery of the white blood cells as much as possible and lower the chance of bleeding and infections.

Graft (donor cells) failure or rejection

The PBSCs or bone marrow (the "graft") might not grow inside your body. There can be a 10 - 15% chance of graft failure. If graft failure happens, this may result in low blood counts for a long period of time. If your counts don't recover, you may need to get a second transplant. Graft failure can be fatal.

Damage to the vital organs in your body

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.

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 the transplant. 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 infection, 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.

Return (relapse) of disease or a new blood cancer

Your disease may come back even if the transplant is successful at first. In rare cases, a new blood cancer may develop from the donor cells.

Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10 years after treatment, or 6 years on average. The risk of developing a new blood cancer after allogeneic transplant is less than 2% (1

or 2 patients (or fewer) out of 100). If cancer develops in your donor's blood cells, you may need more chemotherapy or another transplant.

Lymphoproliferative Syndrome

Patients in treatment Treatment Group A (CD34 Selected Peripheral Blood Stem Cell Graft) have an increased risk of developing post-transplant lymphoproliferative disorder (PTLD) or lymphoma caused by a virus called EBV. They can develop symptoms like fevers and enlarged lymph nodes. Your doctor may use scans and biopsies to confirm the diagnosis. Your blood will be monitored to check if you have signs of EBV in the blood. In many patients EBV can be treated at that stage before it ever progresses to lymphoma. EBV in the blood or EBV lymphoma often responds to treatment with rituximab, a drug commonly used in other lymphomas.

Risk to the Unborn

The treatments in this study have not been proven safe at any stage of pregnancy. If you are pregnant or nursing, you can't join this study. Women who can become pregnant must use effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD, and for 1 year after transplant. 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 cause birth defects if you take them while you are pregnant. It is important that females who aren't pregnant or breast-feeding don't become pregnant while part of the study.

Both women who can become pregnant and their male partners should use birth control for 1 year after transplant while on this study.

- Females who join the study

If you are female 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're in the study. Women who have gone through puberty might experience irregular menstrual cycles or their cycle might stop forever. This doesn't mean that you can't become pregnant. You must still use an effective form of birth control during your

transplant and continue with it until you are finished with GVHD prevention treatment. Be sure to talk with your doctor about options for fertility planning, like storing your eggs, before starting chemotherapy and radiation treatment.

- Males who join the study

If you are male, your body may not be able to produce sperm (become sterile). Be sure to talk with your doctor about options for fertility planning, like banking your sperm, before starting chemotherapy and radiation treatment.

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things that might make you want to stop being in the study. If this happens, we will let you know so you can decide if you want to continue in the study.

Other Treatments or Medicines

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study. For more

information about risks and side effects, ask

your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you can still receive an allogeneic transplant to treat your disease. The treatment and tests could be very similar to what you'd receive if you're part of the 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.

- An allogeneic transplant that is not part of the study, or another type of transplant
- Participation in another research study, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort 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.

8. Possible Benefits

We don't know if taking part in this study will make your health better. The information from this study will help doctors learn more about drugs used to prevent GVHD. This information could help people with a blood cancer who may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn new information about the study drugs 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 participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit 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 these agencies or organizations:

- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC), including The Emmes Corporation
- BMT CTN Data and Safety Monitoring Board (DSMB)
- Miltenyi Biotec, makers of the device that removes cells that are associated with the development of GVHD (used in Treatment Group A)
- 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 clinical trial 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

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

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 too soon after transplant (see **Section 6: Risks and Discomforts**), 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 getting the study treatment, or are asked to leave by your doctor 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

evaluation.

12. Physical Injury as a Result of Participation

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

You will get medical treatment if you are injured as a result of 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 seek 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 Reimbursements

Most of the visits for this study are standard medical care for your allogeneic transplants 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 optional blood samples 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 details]

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 any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[Insert appropriate contact details]

The ethical aspects of this 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 Consent Form is about future research studies. This research will use blood samples from people who are taking part in the main study. You may choose to give blood samples for these 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 immune recovery research studies.

Researchers are trying to learn more about why patients develop side effects after transplant, such as infections and graft-versus-host-disease (GVHD). 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'll collect 5 blood samples from your catheter or a vein in your arm. These samples will probably be collected at the same time as your other blood draws. We'll take about 2 teaspoons (or 6 mL) before you begin the conditioning regimen for

your transplant, and about 20 teaspoons (or 86 mL) at each time: 35 days, 100 days, 6 months, and 1 year after your transplant.

These samples will only be collected from patients who are more than 66 pounds (30 kg).

- 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. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples. A link to this code does exist. The link is stored at the Data and Coordinating Center for the BMT CTN DCC. The staff at the repository where your samples are being stored does not have a link to this code. Your research samples will continue to be stored at the BMT CTN Repository until they are used up for research.
- c.) Materials 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.

Things to Think About:

- The choice to let us have blood samples for future research is up to you. No matter what you decide to do, it will not affect your care.
- If you decide now that your blood can be kept for future research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.
- In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.
- 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.

Genetic Information Nondiscrimination Act:

- A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA), generally 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 that we get from this research.

- This means that they must not use your genetic information when making decisions about your insurance. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits:

The benefits of research using blood include learning more about how your body's immune system recovers after a transplant, as well as why certain complications like graft-versus-host disease or infections develop.

Risks:

There is a small risk of an infection or fainting from the blood draw.

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

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at [\[contact information\]](#).

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

Statement of Consent for Blood Samples for Future Research (Optional)

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 and for research. If I decide not to 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.

- I agree to allow my blood samples to be stored for research.
- I do not agree to allow my blood samples to be stored for research.

Signature

Date

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher’s staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center Phase II Trial of Randomized Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

B. Individual Health Information to be Used or Disclosed:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

The researcher and the researcher’s staff may collect 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 me during the course of the research may be received and used by the following parties:

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH)
- Blood and Marrow Transplant Clinical Trials Network Data and Coordinating Center (BMT CTN DCC) , including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP), and the EMMES Corporation.
- BMT CTN 1301 Co-Principal Investigators: Dr. Leo Luznik, Dr. Marcelo Pasquini, and Dr. Miguel Angel Perales.

Other Organizations

- U.S. government agencies that are responsible for overseeing

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

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.
- Miltenyi Biotec, makers of the device that removes cells that are associated with the development of GVHD (used in Treatment Group A)

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 treatment related to research that is provided through the study.

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 my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. This authorization does not have an expiration date.

Title: BMT CTN #1301: A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-Versus-Host-Disease

Principle Investigator:

Name:

Email:

Address:

Phone:

Fax:

- 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