Informed Consent to Participate in Research

BMT CTN 1703

A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

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BMT CTN 1801

Companion Study: Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune)

Your Name: _____

Study Title: A Randomized, Multi-Center, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

Companion Study: Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune)

Protocol: BMT CTN 1703 / BMT CTN 1801

Principal Investigator: *Insert local PI information*

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

SUMMARY

The following is a consent form for research and a peripheral blood stem cell transplant for which you are eligible.

The research involves 2 questions. The first research question is whether one combination of medications designed to prevent graft-versus-host disease (GVHD) is better than another combination of medications. This question will be answered by the procedures outlined in the BMT CTN 1703 study by comparing Tacrolimus/methotrexate (the standard treatment) versus Tacrolimus/mycophenolate mofetil/cyclophosphamide (the experimental treatment).

The second research question is whether intestinal bacteria and proteins related to them influence transplant outcomes, including the risk of GVHD. This question will be answered by procedures outlined in BMT CTN 1801 involving collection of samples of blood, urine, and stool during the course of this study.

The peripheral blood stem cell transplant is considered standard of care.

Both of these research questions and the transplant are outlined in greater detail below. Your participation in these studies is completely voluntary.

BMT CTN 1703 - A Randomized, Multi-Center, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

Purpose: The purpose of this study is to compare 2 combinations of drugs to prevent graft-versus-host disease (GVHD), a serious complication of a stem cell transplant. These combinations are either Tacrolimus/methotrexate or Tacrolimus/mycophenolate mofetil/cyclophosphamide. Doctors want to know which combination is better or if they give the same results. The study will help doctors decide which treatment is best at preventing GVHD for future transplant patients.

Procedures: Before the transplant, you will have testing to see if you are a suitable candidate for this study and transplantation. You will receive a conditioning regimen chosen by your doctor to prepare your body for transplant. A computer will randomly assign you to 1 of the 2 treatment groups. The treatment will start either before or after you receive the donor's stem cells.

Risks: Most of the risks you may experience are from the medications you will receive and the transplant. More details can be found in the following consent

Benefits: Information from this study may help doctors learn more about medications used to prevent GVHD for future transplant patients.

Duration: You will be in the study for 1 year after your transplant.

BMT CTN 1801 - Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune)

Purpose: The purpose of this study is to understand if the bacteria and proteins in your gut and body fluids can help the doctors predict transplant outcomes.

Procedures: We will collect blood, urine, and stool samples, as well as detailed health information about your infections and antibiotic use. The sample collections will happen before and after your transplant and at your regular clinic visits. Some of these samples will be stored for future research.

Risks: Main risk is loss of confidentiality, but study staff have in place many safeguards for your privacy.

Benefits: Information from this study may help doctors learn more about how the bacteria and proteins in your body could affect a transplant patient's outcome. This information could help to improve the outcomes for future transplant patients.

Duration: You will be in the study for 2 years after your transplant.

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 2 combinations of drugs to see which is better at preventing Graft-versus-Host Disease (GVHD). You are being asked to join this study because:

1. You have a disease that can be treated by a **peripheral blood stem cell transplant**; and
2. Your doctor plans to use a **reduced-intensity conditioning regimen** for your transplant.

You will be in the study for 1 year after your transplant. This study will take at least 3 years and will include 428 participants. There will be 214 participants in each of the treatment groups.

We are also doing a companion study called Mi-Immune with participants enrolled in the main study. We want to understand if the microorganisms and proteins in your immune system can help us predict transplant outcomes. The companion study will take 2 years and will include 300 participants. This study is explained in greater detail in Section 18: Mi-Immune Study Research Samples of this consent.

This Consent Form will tell you about the purpose of the research, the possible risks and benefits, other options available to you, and your rights as a participant in the study. Your study doctor or study nurse will go over this form with you.

Everyone who takes part in this 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'll be given a signed and dated copy to keep. No once can force you to take part in this study.

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 will direct the research study. The BMT CTN and the NIH will make decisions about how to manage the study.

A blood stem cell transplant is a standard treatment for blood cancers such as acute and chronic leukemias, lymphoma and myelodysplastic disorders. It replaces the abnormal (or diseased) blood cells with healthy cells from a donor. It requires a close tissue match between you and the donor. Your donor could be a family member, or it could be an unrelated person. The chemotherapy and radiation you get to destroy the abnormal cells and prepare your body for transplant is called the **conditioning regimen**. When lower doses of chemotherapy and radiation than usual are given, it's called a **reduced-intensity conditioning regimen.**

A common problem that may occur after a blood stem cell transplant is a condition known as Graft-Versus-Host Disease (GVHD). The "graft" is the donor blood cells that you will get during your transplant. The "host" is the person (in this case, you) receiving the cells. GVHD is when the donor graft attacks and damages some of your (the transplant recipient's) tissues.

- GVHD can cause skin rash, stomach (intestinal) problems such as nausea, vomiting, or diarrhea
- It may also damage your liver and cause hepatitis or jaundice (yellowing of the skin).
- GVHD may also increase your risk of infection.

3. Study Purpose

We are inviting you to take part in this study because you have a cancer of the blood or lymph glands and a blood stem cell transplant is a treatment option.

The purpose of this study is to compare 2 combinations of drugs to prevent GVHD. These combinations are listed below.

Group A (current standard of care)	**Group B** (this is being used more often in stem cell transplant)
Tacrolimus and methotrexate	Tacrolimus, mycophenolate mofetil and cyclophosphamide

Doctors want to know which combination (A or B) is better, or if they give the same results. The study will help doctors decide which treatment is best at preventing GVHD for future transplant patients.

4. Right to Ask Questions and/or Withdraw

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

[*insert contact info for Principal Investigator or study team*]

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 can answer your questions about joining or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, while you receive treatment, and for **1 year** after transplant.

Before You Begin the Study

First, you will need to have several tests or check-ups to see if you can be in the study. These exams, tests or procedures are part of regular cancer care. They may be done even if you do not join the study. These include:

- Medical history
- Physical examination, including height and weight
- Blood and urine tests
- Heart function tests, including EKG and ejection fraction
- Lung (pulmonary) function tests
- Tests to evaluate your cancer, including a bone marrow aspirate/biopsy if you have acute leukemia, chronic myeloid leukemia or myelodysplastic syndrome. This is where samples of your bone marrow are taken from your hip bone with a needle.
- Imaging studies if you have lymphoma
- Chest X-ray or chest CT
- A pregnancy test if you are a woman able to have children. If you are pregnant, you will not be able to take part in this study.
- Blood, urine, and stool samples for a Mi-Immune Study (see **Section 18: Mi-Immune Study Research Samples**)

Study Participation

If you decide to join the study, your participation will last for **1 year** after your transplant for the main study. The Mi-Immune study will collect research samples from you at 2 years after your transplant. We will ask you to sign this Consent Form and you will get a copy of the signed form to keep. Most of the tests and procedures used for this study are the same as those normally used for transplant patients. However, there will be some extra tests if you join the study:

1) Questions about your health and how well you can do your normal everyday activities (Patient Reported Outcomes (PRO) surveys). The CIBMTR Survey Research Group will contact you by email, phone or mail to collect PRO surveys online or on paper. Your transplant center will provide your name and contact information to the CIBMTR Survey Research Group when you enroll in the study, so that they may administer the survey to you. You will take the surveys before your conditioning regimen and on Days 98, 180, 365 after your transplant.

2) Mi-Immune biological samples: blood, urine and stool samples

Before the Transplant

Before your transplant, your doctor will choose a conditioning regimen. The conditioning regimen prepares your body for transplant. It uses chemotherapy and/or radiation to destroy the cancer cells and the cells that make up your immune system. Your doctor will decide which regimen you will receive before you are assigned to 1 of the 2 GVHD treatment groups.

Randomization

We will use a computer to randomly assign you to 1 of 2 treatment groups. You will have an equal chance of being in either group. It's just like flipping a coin. You or your doctor won't choose your group. Once you're in a group, you or your doctor can't change your group. Both you and your doctor will know which group you are in.

During Your Transplant

The treatments that are used to prevent GVHD start either before or after you receive the donor stem cells. These treatments are a combination of drugs that hold back (suppress) your immune system and a standard component of the transplant.

Details on the drugs we will give you for both treatment groups are outlined below:

Group A: Tacrolimus and methotrexate	**Group B: Tacrolimus, mycophenolate mofetil and cyclophosphamide**
• Tacrolimus: given daily as a pill by mouth or intravenously (IV) through your vein,	• Tacrolimus: given daily as a pill by mouth or by intravenously (IV) through your

beginning 3 days before your transplant. We will slowly decrease the amount of drug given to you and eventually stop. This process occurs over several months. • Methotrexate: given intravenously (IV) through your vein on 4 different days (1, 3, 6 and 11) after your transplant.	vein, beginning on Day 5 after your transplant. We will slowly decrease the amount of drug given to you and eventually stop. This process occurs over several months. • Mycophenolate mofetil: given daily intravenously (IV) through your vein or as a pill by mouth 3 times a day, beginning on Day 5 after your transplant, and will continue for 30 days. Your doctor may decide to continue this drug if you still have GVHD. • Cyclophosphamide: given intravenously (IV) through your vein, over 1-2 hours, on Day 3 and Day 4 after your transplant.

Peripheral Blood Stem Cell Transplant

On your transplant day, the stem cells will be given to you through your central line, like a blood transfusion. The cells will travel through your bloodstream to your bone marrow where they will start to make healthy, new blood cells after several weeks.

Health Evaluations After the Transplant (see Table 1)

We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving transplant except for the PRO questions and the Mi-Immune research samples. This means they would be done even if you were not part of this study. The exceptions to this are the PRO questions described above and the Mi-Immune research samples. You will be watched closely for any signs and symptoms of GVHD.

- Physical exam to assess toxicities, and infections weekly until Day 84 and then at Days 98, 180, 270 and 365.
- Physical exam to assess GVHD weekly starting Day 7 until Day 84 and then at Days 98, 180, 270 and 365.
- Routine blood tests (cell counts, liver and kidney function) weekly until Day 84 and then at Days 98, 180, 270, 365 and 730.
- Blood or bone marrow tests to find the amount of donor cells in your body on Days 28 and 98. This is also called *chimerism.*
- Disease evaluation tests to see how much cancer you have after treatment on Days 98 and 365.

- **Mi-Immune research samples:** Blood, urine, and stool samples for the Mi-Immune study and future research collected weekly through Day 84, then at Days 98, 180, 270, 365 and 730 (see Section 18: Samples for Additional Research). Mi-Immune research samples: the stool samples at Pre-Conditioning, Day 0, Day 7, Day 14, Day 21, and Day 28 are mandatory. Starting day 35 through day 77, then at day 98, 180, 270, 1 year, and 2 years, the stool samples are optional. Weekly urine sample collection for Pre-conditioning through Day 270, then at 1 year, and 2 years are ALL OPTIONAL.

Table 1: Schedule for Health Evaluations after Transplant

	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 98**	**Day 180**	**Day 270**	**Day 365**	**Day 730**
Medical history, physical exam, & weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC & chemistries	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete GVHD assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infection assessment		X		X		X		X		X		X		X	X	X	
Disease evaluation													X			X	
Patient Reported Outcome surveys													X	X		X	
Mi-Immune research samples (see Table 4)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to life-threatening. The risks and discomforts from this study are similar to what you would have even if you do not join this study. If you do, the effect on you might be better, worse or about the same. Your health care team may give you medicines to help lessen side effects such as feeling sick to your stomach (nausea). In some cases, side effects can be long lasting or may never go away.

Risks of Medicines

All of the immune suppressive and conditioning regimen drugs listed below are commonly used in blood stem cell transplant. The tables below describe all conditioning regimens that are allowed to be used in this study. The regimen you will receive depends on your doctor's choice.

Table 2: Conditioning Regimens

Reduced Intensity Conditioning	Nonmyeloablative Conditioning
Fludarabine/Busulfan (Flu/Bu) • Fludarabine (120-180 mg/m^2) • Busulfan (less than or equal to 8 mg/kg PO or 6.4 mg/kg IV)	**Fludarabine/Cyclophosphamide (Flu/Cy)** • Fludarabine (90-120 mg/m^2) • Cyclophosphamide (120 mg/kg or 2250 mg/m^2)
Fludarabine/Melphalan (Flu/Mel) • Fludarabine (120-180 mg/m^2) • Melphalan (less than or equal to 150 mg/m^2)	**Fludarabine /Total Body Irradiation (Flu/TBI)** • Fludarabine (90 mg/m^2) • TBI (200 cGy)
	Fludarabine/ Cyclophosphamide/TBI (Flu/Cy/TBI) • Fludarabine (150 mg/m^2) • TBI (200 cGy) • Cyclophosphamide (29-50 mg/kg)

Table 3: Risks and Side Effects

Likely	This side effect is expected to happen in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	This side effect is expected to happen in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	This side effect does not happen often – in fewer than 3% of patients – but is serious when it happens. This means that 0, 1, 2 or 3 patients out of 100 might get this side effect.

Methotrexate

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 3%)	**Rare, but Serious** (May happen in 3% or fewer patients)
▪ Increased risk of sunburn or rash ▪ Nausea, vomiting, loss of appetite ▪ Sores in mouth which may cause difficulty swallowing	▪ Anemia from low red blood cell count which may cause tiredness, or may require transfusion ▪ Blood clots which may cause swelling, pain, shortness of breath ▪ Bruising, bleeding from low platelet count ▪ Diarrhea, sores in the gastrointestinal tract ▪ Fluid around the heart ▪ Hair loss ▪ Hepatitis or liver damage which may cause yellowing of eyes and skin, generalized swelling ▪ Infection, especially when white blood cell count is low ▪ Kidney damage	▪ A new cancer ▪ Internal bleeding which may cause belly pain, black tarry stool, blood in vomit ▪ Scarring of the lungs which may cause shortness of breath, confusion ▪ Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Mycophenolate Mofetil (MMF, Cellcept®)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 3%)	**Rare, but Serious** (May happen in 3% or fewer patients)
▪ Birth control may not work as well ▪ Damage to unborn baby if you become pregnant while taking this medicine ▪ Difficulty breathing, cough ▪ Headache ▪ High blood pressure ▪ Low white blood cell count with increased risk of infection ▪ Nausea, vomiting, diarrhea, stomach pain ▪ Swelling of the hands, feet, ankles, or legs ▪ Tremors	▪ Anemia (low red blood cell count) ▪ Change in the levels of salts in the blood ▪ Decreased platelet count, may cause blood loss into stool or vomit, increased bruising ▪ Difficulty falling asleep or staying asleep ▪ Dizziness ▪ Low blood pressure ▪ Pain in joints or muscles ▪ Rash	▪ A new cancer ▪ Change in vision ▪ Encephalopathy or brain dysfunction that can lead to death ▪ Excessive tiredness ▪ Fast heartbeat ▪ Progressive Multifocal Leukoencephalopathy – This is caused by a virus that damages the protective covering in the brain. ▪ Severe difficulty breathing ▪ Weakness

Tacrolimus (FK506, Prograf®)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 3%)	Rare, but Serious (May happen in 3% or fewer patients)
▪ Abnormal body movement, including tremors ▪ Abnormal levels of sugar, fat, or minerals (like sodium or potassium) in your blood ▪ Constipation, diarrhea, nausea, vomiting, reflux, lack of desire to eat ▪ Difficulty sleeping ▪ Dizziness ▪ Feeling of "pins and needles" in arms and legs ▪ Headache ▪ High blood pressure which may cause dizziness, chest pain ▪ Itching, rash ▪ Kidney damage which may cause swelling, may require dialysis ▪ Low red blood cell counts, which may cause tiredness, or may require blood transfusions ▪ Low platelet levels, which may cause bruising, bleeding ▪ Low white blood cell counts, which may lead to infection ▪ Liver damage ▪ Swelling of the body	▪ A new cancer ▪ A tear or a hole in your bowels which may cause belly pain and may require surgery ▪ Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat ▪ Change in the heart rhythm, abnormal heartbeat, or heart stops beating ▪ Damage to brain, which may cause headache, seizure, blindness ▪ Damage to lungs, which may cause shortness of breath, fluid around lungs ▪ Heart attack or heart failure which may cause chest pain, swelling of ankles, and tiredness	▪ Damage to small blood vessels with resulting small blood clots and possible organ damage.

It is very important that you <u>do not eat grapefruit or drink grapefruit juice</u> 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*.

Cyclophosphamide (Cytoxan®)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 3%)	**Rare, but Serious** (May happen in 3% or fewer patients)
▪ Absence of menstrual cycles which may decrease the ability to have children ▪ Blood in urine ▪ Feeling tired ▪ Hair loss, skin changes, rash, change in nails ▪ Infection, especially when white blood cell count is low ▪ Nausea, vomiting, diarrhea, loss of appetite, pain in belly ▪ Sores in mouth	▪ Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat ▪ Decrease in platelets which may cause bleeding ▪ Decrease in red blood cells, which may require blood transfusions ▪ Loss or absence of sperm which may lead to an inability to father children	▪ A new cancer ▪ Damage to the heart or heart failure which may cause shortness of breath, swelling, cough or tiredness ▪ Scarring of the lungs which may cause shortness of breath, fluid arounds the lungs ▪ Swelling of the brain which may cause dizziness, confusion

Busulfan

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 3%)	Rare, but Serious (May happen in 3% or fewer patients)
• Abnormal or fast heartbeat • Abnormal salt and/or vitamin levels that may require IV fluids • Anemia (low red blood cells) which may require blood transfusions • Chills, fever • Constipation, diarrhea, heartburn, nausea, vomiting, loss of appetite, stomach pain • Cough, stuffy nose • Damage to the liver or kidneys • Difficulty sleeping • Dizziness, headache • Feeling tired • High blood pressure • Infection, especially when white blood cell count is low • Low platelet counts which may cause bruising or bleeding • Pain • Rash • Sadness, worry • Sores in mouth which may cause difficulty swallowing • Swelling of the body	• Blood in the urine • Coughing up blood • Damage to or scarring of the lungs • Loss or absence of sperm • Menopause • Seizure • Visual disturbances	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Fluid around the heart • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Low blood pressure which may cause feeling faint

Fludarabine

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 3%)	Rare, but Serious (May happen in 3% or fewer patients)
• Anemia (low red blood cells) which may require blood transfusions • Cough • Feeling tired or irritable • Infection, especially when white blood cell count is low • Low platelet counts, which may cause bruising or bleeding • Pain	• Chills • Confusion • Damage to brain, lungs, or other organs. This may cause tiredness, changes in thinking or shortness of breath • Feeling of "pins and needles" in arms and legs • Nausea, vomiting, loss of appetite • Sores in mouth which may cause difficulty swallowing	• Blood in urine • Changes in vision • Kidney damage which may require dialysis • Liver damage • Seizures

Melphalan

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 3%)	Rare, but Serious (May happen in 3% or fewer patients)
• Anemia (low red blood cells) which may require blood transfusions • Diarrhea • Feeling tired • Infection, especially when white blood cell count is low • Nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Swelling of the body	• Inflammation of blood vessels • Kidney problems which may require dialysis • Liver problems which may cause yellow eyes or skin • Low platelet counts, which may cause bruising or bleeding • Scarring of the lungs which may cause shortness of breath	• A new cancer • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness

Low Dose Total Body Irradiation (TBI)

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 3%)	Rare, but Serious (May happen in 3% or fewer patients)
• Anemia (low red blood cells) which may require blood transfusions • Infection, especially when white blood cell count is low • Low platelet counts, which may cause bruising or bleeding • Mouth sores • Nausea, vomiting, stomach pain, diarrhea	• Eye cloudiness • Hair loss • Inability to have children • Painful swelling of the salivary glands under the ears for a few days • Redness of the skin	• A new cancer • Back pain • Difficulty swallowing • Hormone problems (such as thyroid disease or diabetes) • Kidney problems • Learning problems • Liver problems • Lung inflammation • Slow growth (for example, height)

Risks and Toxicities Related to Transplant

Everyone who has a stem cell transplant faces these risks. These are serious, and in some cases can cause death. These risks are **not** specific to this study.

Slow recovery of blood counts: The red blood cells, white blood cells, and platelets can be slow to recover after blood or marrow transplant. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. You may receive filgrastim, a medicine to help speed up the recovery of white blood cells.

Graft failure: The stem cells from your donor (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 10-15% chance of graft failure. Graft failure may cause low blood counts for a long time. If your counts do not recover, you may need to receive a second transplant. Graft failure can be fatal.

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 or difficult to treat and may lead to death. You will be watched closely for this complication and given drugs to prevent and/or treat it.

Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a

biopsy (a small sample of your tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

Other complications. Other complications may include:

a. Damage to the vital organs in your body. The transplant could cause problems in any body organ such as the heart, lungs, liver, gut, kidneys and bladder, or brain. The kidneys and the liver are most likely to be damaged. Some patients will experience serious lung problems from infections, chemotherapy or radiation.

b. Serious infections. Full and complete recovery of your immune system may take many months. During this time, there is an increased risk of infections. You will take medicines to lower your risk of infections. However, these treatments do not always work. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections may result in death.

c. Relapse of disease or a new blood cancer. Your leukemia or lymphoma may come back even if the transplant is initially successful. 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 blood or marrow transplant is probably less than 2%. If cancer develops in your donor's blood cells, you may require additional treatment with chemotherapy or another blood or marrow transplant.

d. Risk to the unborn. The treatments in this study have <u>not</u> been proven to be safe at any stage of pregnancy and could affect the health of infants exposed to them via mother's milk. Therefore, if you are pregnant or nursing, you are not eligible for 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 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 1 year after transplant while on this study.

- **If you're 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 during your transplant and continue until you are finished with your GVHD prevention treatment. You may want to talk with your doctor about ova banking before having a transplant.

Effective birth control is defined as the following:

1. Not have any vaginal sex (abstinence)
2. Consistently use birth control pills or patch
3. Use injectable birth control (for example, Depo-Provera or Norplant)
4. Have tubal sterilization (tied tubes)
5. Have 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 and will watch you closely if you become pregnant.

- **If you're male:**

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

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 use:

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 of a 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.

Additional Information about MMF

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
- MMF can make birth control pills not work well. So, you have a **higher** risk of becoming pregnant while you are taking it.
- If you could become pregnant, you **must** use 2 effective forms of birth control for 4 weeks before starting MMF, during treatment, and for one year after transplant.

If you think you might be pregnant or could become pregnant prior to enrollment, you should **not** join this study.

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. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things about reduced-intensity transplants that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study. There may be some unknown or unanticipated discomforts or risks associated with this treatment in addition to those specified above, but every precaution will be taken to assure your personal safety and to minimize discomforts.

Other Treatments or Medications

Some medicines react with each other, so 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 these medicines while you're in the study.

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

Patient Reported Outcomes surveys

There are a few risks from completing the quality of life surveys. Some of the questions or topics may upset you. You may feel emotional or that your privacy is lost. Talk to your doctor about your privacy concerns. We can put you in touch with a counselor or trained support specialist, if needed.

7. Alternative to Participation

Participation in this study is optional. If you choose not to take part, you may still receive a transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study. Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant.
- A transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood 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

Taking part in this study may or may not make your health better. The information from this study could help doctors learn more about medications used to prevent GVHD.

9. New Information Available During the Study

During this study, the study doctors may learn about new information about the study drugs or the risks and benefits of taking part in the study. If they learn new information, they'll tell you as soon as it's available. The new information may mean that you can no longer participate in the study, or you may not want to continue.

10. Privacy, Confidentiality, and Use of Information

Your privacy is very important to us. The study doctors will make every effort 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 given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify you.

Representatives from government agencies, including the U.S. Food and Drug Administration ("FDA"), institutional review boards, the Sponsors and/or the Sponsors' authorized representatives may need access to your original medical records and study records to check information collected for the study. By signing this Consent Form, you authorize this access.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your study number (code) is not related to your name, social security number, or medical record number at [insert facility name]. Coded study information may also be used for unexpected medical projects and research in the future. These projects could be related to **your disease or similar diseases, and development of the study drug.** At all times the projects will follow the law.

You will not be able to access your personal health information related to this study until the study is done. This helps to maintain the scientific integrity of the study.

After the study is complete, you can ask your study doctor for your health information. By signing this Consent Form, you agree to ask for your health information only after the study is done.

Information about your transplant from your original medical records may be seen or sent to:

- 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 National Marrow Donor Program (NMDP)/Be The Match registry and The Emmes Corporation, 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 [Institution]
- Institutional Review Boards (IRBs) responsible for this study

Data about your clinical situation, including follow-up after 1 year, may be obtained by the BMT CTN from the CIBMTR. The CIBMTR collects information on all U.S. transplants.

We won't identify you by name in any publications or reports that come from these organizations or agencies.

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. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

The study doctor or the study sponsor may stop the study at any time. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. 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.

Even if you leave the study, the information collected from your participation will be included in the study evaluation. If you don't want any of your information to be used or if you want to cancel this authorization, you must let your study doctor know.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor or study staff if you feel that you have been hurt or injured because of taking part in this study.

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 sponsor will not pay for medical treatment.

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

13. Compensation or Payment

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

14. Cost and Reimbursement

Most of the visits for this study are standard medical care for patients undergoing allogeneic transplants and will be billed to your insurance company. You and/or your health insurance company will need to pay for some or all of the costs of standard 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'll pay.

You or your health plan/insurance will not be charged for optional research samples on this study.

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

15. Ethical Review

The ethical aspects of this research study have been reviewed and approved by the National Marrow Donor Program IRB.

16. For More Information

If you would like more information about this study, or if you have problems while you are participating in this study, you can contact the study doctor or staff.

[*Insert name and contact details*]

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

17. Independent Contact

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

[Insert appropriate contact details]

18. Mi-Immune Study Research Samples

For the Mi-Immune study, we are collecting health information and extra blood, urine and stool samples from transplant patients. We want to understand if the microorganisms and proteins in your immune system can help us predict transplant outcomes.

The protocol-defined studies include testing the microorganisms in your stool, the metabolism waste in your urine and the proteins found on your white blood cells in your blood. Some of the samples will be stored for future research.

You will be in the study for 2 years after your transplant. This study will include 300 participants.

Here is what will happen:

a.) We will collect blood, urine, and stool samples before and after transplant (see Table 4). The collections will happen at your regular visits. Stool samples at Pre-Conditioning, Day 0, Day 7, Day 14, Day 21, and Day 28 are mandatory. Starting day 35 through day 77, then at day 98, 180, 270, 1 year, and 2 years, the stool samples are optional. Weekly urine sample collection for Pre-conditioning through Day 270, then at 1 year, and 2 years are ALL OPTIONAL.

b.) The samples 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 coded with a unique code. The codes themselves do not contain information that could identify you, however, a link to this code does exist. The link is stored at the Data and Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC). The staff at the Repository where your sample is 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 approved research.

c.) We will use your health information from the main study BMT CTN 1703 and CIBMTR but will collect additional data, such as infection and medication information.

Samples stored in the Repository will be used mainly by doctors and researchers in the BMT CTN network. In the future, the unused blood samples and health information will be made available outside of this network. Researchers can apply to study the health information and samples 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.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

Risks Related to Research Samples

The risk of injury is small. If your blood samples are collected from your arm (instead of your central line), you may bleed a little bit and/or develop a small bruise. Infection from blood draws is rare, but may happen. If you are uncomfortable at the sight of blood, you may feel light-headed or faint.

There are no major risks to collecting your urine or stool samples. A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and health information to make sure that your personal information will be kept private. It's very unlikely that your personal information will be given to someone else (see the Privacy, Confidentiality and Use of Information section below).

Table 4. Timeline for Collection of Research Samples

Tests and Samples during Study	Before conditioning	Pre-Infusion Day -1 or 0	Weekly, Day 7-77	Day 84	Day 98	Day 180	Day 270	Day 365	Day 730
Blood samples	X 39ML (8 TSPS*)	X 24ML (5 TSPS)	X 31ML OR 39ML (6 OR 8 TSPS)	X 31ML (6 TSPS)	X 39ML (8 TSPS)	X 39ML (8 TSPS)	X 31ML (6 TSPS)	X 39ML (8 TSPS)	X 39ML (8 TSPS)
Urine samples[1]	X[1] 10-12ML (3 TSPS)	X[1] 10-12ML (3 TSPS)	X[1] 10-12ML (3 TSPS)		X[1] 10-12ML (3 TSPS)	X[1] 10-12ML (3 TSPS)	X[1] 10-12ML (3 TSPS)	X[1] 10-12ML (3 TSPS)	X[1] 10-12ML (3 TSPS)
Stool samples[2]	X[2] 10-12ML (3 TSPS)	X[2] 10-12ML (3 TSPS)	X[2] 10-12ML (3 TSPS)		X[2] 10-12ML (3 TSPS)	X[2] 10-12ML (3 TSPS)	X[2] 10-12ML (3 TSPS)	X[2] 10-12ML (3 TSPS)	X[2] 10-12ML (3 TSPS)

*TSPS = Teaspoons

[1] Weekly urine sample collection for Pre-conditioning through Day 270, then at 1 year, and 2 years are ALL OPTIONAL.

[2]Stool samples at Pre-Conditioning, Day 0, Day 7, Day 14, Day 21, and Day 28 are mandatory. Starting day 35 through day 77, then at day 98, 180, 270, 1 year, and 2 years, the stool samples are optional.

Genome-Wide Association Studies:
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 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.

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 regarding insurability. 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.

Things to Think About:

- The choice to let us have blood/urine/stool samples for protocol-defined studies and stored 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/urine/stool can be kept for 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/urine/stool sample. Then any blood/urine/stool that remains will no longer be used for research.

- In the future, people who do research on these blood/urine/stool 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.

- Sometimes blood/urine/stool is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

- Your blood/urine/stool will be used only for research and will not be sold. The research done with your blood/urine/stool may help to develop new products in the future.

- Reports about research done with your blood/urine/stool will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Benefits:
The research that may be done with your blood/urine/stool is not designed specifically to help you. The benefits of research using blood/urine/stool include learning more about what causes GVHD, cancer and other diseases, how to prevent them, and how to treat them.

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.

The results of this study will be published, but your personal information (for examples, name and address) will remain confidential (private). BMT CTN may also use the information from this study for future medical research.

♦ ♦

Health Insurance Portability and Accountability Act 1 (HIPAA[1]) 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:

[List PI and research staff]

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:

Principal Investigators and the researchers' staff

BMT CTN 1703: Drs. Javier Bolaños-Meade and Shernan Holtan, Co-Principal Investigators

BMT CTN 1801: Drs. Ami Bhatt, Leslie Kean and Miguel Perales, Co-Principal Investigators

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),

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

- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and The Emmes Corporation, who are coordinating the studies of the BMT CTN
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for this study

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 1703: A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Hematopoietic Cell Peripheral Blood Stem Cell Transplantation

COMPANION STUDY: BMT CTN 1801: Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune)

Principal Investigator(s)

Name: Phone:

Address: Fax:

Email:

- I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.
- I have had the chance to ask questions and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified, and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed Consent Form.
- I understand that I will be participating in the Companion Study – Mi-Immune and that I will have blood, stool and urine samples collected.

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 Person Obtaining Consent	Date
Signature of Person Obtaining Consent	Date