IRB #

Informed Consent to Participate in Research

Principal Investigator Contact Information
(Insert contact information for PI at your site)

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

Introduction
This is a clinical trial, which is a research study to answer specific medical questions. The information from this study will help future patients. The Study doctor (the person in charge of the research) will explain the clinical trial to you. Clinical trials include only people who choose to join the study.

Please take your time to decide if you want to join this study. Some people find it helpful to talk about the study with their family and friends before they make a decision. It may also be useful to talk with your doctor and other people on your health care team about the study. If you have questions or want to know more about the study, you can ask them for more information.

You are asked to join this study because:

1. You have a disease that can be treated by a peripheral blood stem cell transplant; and,
2. You have a brother or sister who has agreed to be your donor.

Before you decide whether or not to join the study, please read the information below. Feel free to ask questions to understand your rights and protections. Participating in this study is your choice. If you decide not to be in this study**,** you and your doctor will discuss other treatment options.

Why is this study being done?
Stem cell transplantation is a standard therapy for acute and chronic leukemias and myelodysplastic disorders. A common problem that may occur after a stem cell transplant is a condition known as graft-versus-host disease (GVHD). The word "graft" refers to the donor blood cells that you will receive during your transplant. The word "host" refers to the person (in this case, you) receiving the cells. GVHD is a complication where the donor graft attacks and damages some of your (the transplant recipient's) tissues.

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

The purpose of this study is to compare two combinations of medications to see which is better at preventing GVHD. These combinations of medications in this study are:

A- Sirolimus and tacrolimus

B- Methotrexate and tacrolimus.

Doctors want to know if combination A is better than combination B or if they give the same results. The study will help doctors make GVHD treatment choices for future transplant patients.

How many people will take part in the study?
About 312 people throughout the country will take part in this study. Each study group will have 156 patients.

What will happen if I take part in this research study?
Before you begin the study -- You will need to have several exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor with the study.

- Medical history and physical exam, including height and weight
- Blood tests
- Urine tests
- Heart function tests
- Lung tests, including a Pulmonary Function Test (PFT)
- Bone marrow biopsies and aspirates

- If you are a woman able to have children, a pregnancy test will also be performed, using a blood sample. If you are pregnant, you will not be able to take part in this study.

Before your transplant, your doctor will choose from one of two conditioning regimens. The conditioning regimen prepares your body for transplant. It uses treatments such as chemotherapy and radiation to destroy the cancer cells and the cells that make up your immune system. Your doctor will decide which conditioning regimen you will receive before you join one of the study groups.

During the study **--** If the exams, tests and procedures show that you can be in the study, the next step is for you to be randomized into one of the study groups described below. Randomization means that you are put into a group by chance, similar to the flip of a coin. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in.

You will begin your conditioning chemotherapy and/or radiotherapy several days prior to the transplant. The treatments to prevent GVHD will begin three days before transplantation for both study groups.

A. Sirolimus/tacrolimus group:

- You will take a sirolimus pill by mouth once per day.
- Tacrolimus will be given **by intravenous infusion (through your vein)** every day while in the hospital.
- Before you leave the hospital the tacrolimus will be changed to a pill that you will take by mouth.
- These medications will be continued for at least 100 days from the time of transplantation.
- The amount of drug given will slowly be decreased and eventually stopped. This process occurs over several months.

B. Methotrexate/tacrolimus group:

- Tacrolimus will be given **by intravenous infusion (through your vein)** every day while in the hospital.
- Before you leave the hospital the tacrolimus will be changed to a pill that you will take by mouth.
- You will take methotrexate on 4 separate days. The methotrexate will be given by intravenous infusion on the 1st, 3rd, 6th and 11th days after your transplant.
- The tacrolimus will be continued for at least 100 days from the time of transplantation.

- The amount of drug given will slowly be decreased and eventually stopped. This process occurs over several months.

Peripheral blood stem cells from your donor will be given to you 3 days after starting the GVHD treatments.

Following the transplant, you will have the following **standard** tests and evaluations:

- Medical history
- Physical examination, including height and weight
- Blood tests
- Urine tests

You will have the following **study** tests performed:

- Blood tests to measure the levels of sirolimus and tacrolimus
- Blood tests to measure your cholesterol and triglycerides (fat) levels
- Oral exams to measure any side effects that occur in your mouth and throat (mucositis)

You will be asked to return to the transplant center for regular follow up care. The standard tests and study tests will be done at that time.

How long will I be in the study?
You will be in the study for up to two years. You will need to take medication for at least 3 months and possibly longer depending on how long it takes to gradually take you off of the medication. You will also need to answer questions about your medical health at regular times for up to two years.

Follow-up for your transplant will last as long as you require care. However, we would like to keep track of your medical condition for the rest of your life by contacting you and the doctor providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study and transplantation in general. Many transplant centers include this type of long-term follow-up as part of their regular medical care. It is not necessary for you to agree to follow-up for longer than two years to participate in this study.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

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

Can the Principal Investigator withdraw me from the study?
You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- You need a medical treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant and the study treatment could be harmful to the fetus.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the dose of study drug you are taking has been found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).

What side effects or risks can I expect from being in the study?
Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Potential Side Effects and Risks from Study Drugs

Sirolimus and Tacrolimus	
Likely (10-25%)	**Less Likely but Serious (< 10%)**
• Elevation of blood lipids (fats, including cholesterol and triglycerides) • Mild reduction in blood counts, including platelets, red cells (anemia) and white blood cells • Low blood potassium • Muscle aches and pains • Fluid retention • High blood pressure • Tremor • Swollen gums • Increased facial hair	• Lung inflammation • Reversible kidney damage, which may lead to acute kidney failure and require hospitalization, possibly dialysis and may lead to permanent kidney failure • Thrombotic Microangiopathy, a syndrome comprised of abnormal kidney function and destruction of red blood cells and platelets. Temporary dialysis may be required for the kidney failure • Neurological dysfunction, including a decreased level of consciousness, coma, blindness and seizures • Veno-occlusive disease, which causes severe damage to the liver

Methotrexate and Tacrolimus	
Likely	**Less Likely but Serious**
• Delay in the time it takes for your blood counts to recover. This may increase the risk of infection and bleeding after transplantation, may increase the number of transfusions required during the transplantation and may prolong your hospital stay. • Worsening of mucositis (inflammation of the lining of the mouth, throat and stomach) • Low blood potassium • Muscle aches and pains • Fluid retention • High blood pressure • Tremor • Swollen gums • Increased facial hair	• Lung inflammation • Reversible kidney damage, which may lead to acute kidney failure and require hospitalization, possibly dialysis and may lead to permanent kidney failure • Thrombotic Microangiopathy, a syndrome comprised of kidney dysfunction and destruction of red blood cells and platelets. Temporary dialysis may be required for the kidney failure • Neurological dysfunction, including a decreased level of consciousness, coma, blindness and seizures

These side effects usually get better completely after you stop taking the drugs, but some long-term problems, such as kidney damage, may occur.

A standard combination of medications to prevent GVHD is the combination of tacrolimus and methotrexate. We are trying to determine if the combination of sirolimus and tacrolimus is as effective as tacrolimus and methotrexate. Because this is a comparative trial to study how to prevent GVHD, there is a risk that you will receive a less effective GVHD prevention program than the standard combination. Even though this study is trying to prevent GVHD from developing, there is a chance that you will still develop GVHD, no matter which combination you receive. All study participants who develop GVHD will be treated for GVHD. The treatment you receive will be up to your doctor.

Refer to Attachment A for additional risks and toxicities for all transplant patients.

Are there benefits to taking part in the study?
There may or may not be direct benefits to you from participating in this study. We hope that information gathered in this trial will benefit future transplant patients.

What other choices do I have if I do not take part in the study?
If you do not want to join this study, you should know your other options. These options include:

- Bone marrow transplantation
- Peripheral Blood Stem Cell Transplantation using standard treatment (but not included in study)
- No transplant
- Other chemotherapy
- No therapy for your cancer with care to help you feel comfortable

You should know about your treatment choices before you decide if you will take part in this study.

What are the costs of taking part in this study?
You and/or your insurance company will pay all standard care relating to your stem cell transplant.

You will not be billed for any tests or procedures that are only for research.

You will not be paid to be in this study.

Sirolimus will be provided free of charge by Wyeth, Inc for at least 6 months. At that time, you or your insurance carrier will responsible for the costs of this medication. Methotrexate and tacrolimus will be the responsibility of you or your insurance carrier.

The companies that make the drugs used in this study did not plan or design this clinical trial. They will also not have a part in analyzing the results of this study.

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.

What if I am injured as a result of being in this study?
In the event that this research activity results in an injury, treatment will be available including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to your insurance company. If you think you have suffered a research related injury, let the study physicians know right away. Unexpected side effects or accidents might result in your getting sicker than anticipated in the course of this treatment. All available medical care will be provided to you, but you and your insurance company (3rd party payer) are responsible for the costs of all such care. If you have any questions about study-related injuries, you may contact [insert name of person at institution] at [insert phone number].

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

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

If you have questions about your rights as a study subject, you may call the Institutional Review Board (IRB) office at [insert phone number].

Will my medical information be kept private?
All necessary steps will be undertaken to avoid your being identified in any public presentations. However, the results of this study treatment may be published in scientific journals in the future, but no one patient (including you) will be identified. Information concerning your transplant course may be reviewed or transmitted to national and international transplant registries, including the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMDP), to the Food and Drug and Administration (FDA), Data Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the EMMES Corporation (which is helping to coordinate this study) and to other authorized study organizations. However, you will not be identified by name in publications or reports coming from such groups or review.

Information related to or resulting from your stem cell transplant will be reported to the CIBMTR. The CIBMTR is a voluntary organization of basic and clinical scientists working together in an effort to gather information on results of stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

HIPAA[1] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Phase III Randomized, Multicenter Trial Comparing Sirolimus/Tacrolimus with Tacrolimus/Methotrexate as GVHD Prophylaxis After HLA-Matched, Related Peripheral Blood Stem Cell Transplantation.*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results).

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

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain 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 researcher's staff, including Dr. Corey Cutler and Dr. Joseph Antin, Study Chairpersons and staff/laboratories at Dana Farber Cancer Institute
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating Center
- 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 responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.
- Others:

_____

_____

_____

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of 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. DNA from your stored blood sample might be used in genome-wide association (GWA) or pharmacogenomics 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 identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease. Pharmacogenomics studies are similar genetic tests but look specifically at genes related to how the body breaks down medications.

i. 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.

   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.

j. This authorization does not have an expiration date.

* *

About Using Blood for Research

Please note: This section of the informed consent form is about future research studies that will be done using blood samples from people who are taking part in the main study described above. You may give small blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to giving blood samples for future

research studies. You can say "yes" or "no" to giving blood samples for future research studies. Please mark your choice at the end of this section.

We would like to have six small (3 teaspoons or 16 mL) blood samples for future research. Patients less than 12 years old will provide 1½ teaspoons or 8 mL). If you agree, these samples will be obtained at the time other blood samples are drawn on 6 occasions pre-transplant and on Day 28, 100, 180, 365 and 730. They will be kept and may be used in research to learn more about GVHD, cancer and other diseases. Usually the blood can be drawn from your central venous catheter at the time of the other blood collections. If this is not possible, it will be taken from a vein. When the sample is given to investigators for research, no information about your name, address, phone number or other information that will let the researcher know who you are will be provided.

The samples collected for research purposes will be sent to the National Heart, Lung, and Blood Institute (NHLBI) sample repository in Maryland. The samples will be labeled with unique codes that do not contain information that could identify you. 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). The staff at the repository where your sample is being stored does not have a link to this code. Your samples will be stored at this repository until the samples have been used for the research tests or until the end of the study. Any research performed on the samples must first be approved by an advisory panel at the NHLBI.

The research that may be done with your blood is not designed specifically to help you. It might help people who have GVHD, cancer and other diseases in the future.

Reports about research done with your blood 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.

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 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.

Sometimes blood 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 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.

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

Risks: 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 ____________________.

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

- ❑ Yes, I agree to have small blood samples drawn for future research.

- ❑ No, I do not agree to have small blood samples drawn for future research.

_______________________________________ _______________________________

Signature *Date*

* *

If you have any questions about this study, you may contact the study Principal Investigator listed on the first page of this form.

If you have questions about your rights as a research participant, you may contact (INSERT CONTACT INFORMATION)

IRB #

CONSENT AND ASSENT INSTRUCTIONS

CONSENT: Subjects 18 years and older must sign on the subject line below. For subjects under 18, consent is provided by the Legally Authorized Representative.

ASSENT: Is required for subjects under the age of 18, using the Assent Section on the following page.

I have been informed about this study's purpose, procedures, possible benefits and risks. I have been given the chance to ask questions. My questions have all been answered satisfactorily. I understand that I can ask other questions at any time.

I voluntarily agree to take part, or to allow my child to take part, in this study.

By signing this consent form, I have not given up any of the legal rights that I (my child) otherwise would have as a subject in a research study.

_____ _____
Subject's Signature Date

If you are not the subject, please print your name_____
and indicate one of the following:

_____	The subject's parent	_____	The subject's guardian
_____	A surrogate	_____	A durable power of attorney
_____	A proxy	_____	Other, please explain:

_____ _____
Legally Authorized Representative Signature Date

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____ _____
Signature of person conducting informed consent Date

ASSENT SIGNATURES: For subjects under the age of 18 years.

Assent of Minor

I have been told what I will be asked to do if I am in this study. I have been told that I don't have to be in this study. I may quit the study at any time, and no one will be mad at me. I have had a chance to discuss the study and ask questions. My questions have been answered. I agree to be in the study and do what I am asked to do so long as I continue in the study.

_____ _____ _____

Signature of Minor Date Age (years)
Study Personnel

I have explained the purposes, procedures, and risks involved in this research study in detail to:

_____

Print name(s) of Parents/Authorized Consenting Party, and

who in my opinion _____IS/____IS NOT capable of assenting to participate in this study.

Print child's name

_____ _____

Signature of Person Conducting Assent Date

ATTACHMENT A

Additional Risks and Toxicities Related to the Standard Transplant Procedure

There are certain risks related to a peripheral blood stem cell (PBSC) transplant. There are risks from the medications and/or irradiation therapy you will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your doctor may give you medications to lessen some of the side-effects.

Risks Related to the Transplant Conditioning Regimen

You and your doctor will choose a conditioning regimen that may include some of the following therapies.

Cyclophosphamide (Cytoxan): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. Cyclophosphamide may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss, short-term bladder problems, and, at times, bleeding from the bladder. A few patients may have bladder damage and bleeding for a longer time. You will be given large amounts of a sterile solution through your central line to protect your bladder. A bladder catheter (thin plastic tube) may be inserted into your bladder, if your physician thinks that it can help you. Cyclophosphamide slows the making of new red blood cells, white blood cells, and platelets. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. Cyclophosphamide also lowers your defense system. As a result, you may have more infections for several months after transplant. In a small number of patients, cyclophosphamide can damage the heart muscle causing heart failure. Sometimes cyclophosphamide causes abnormal heart function. If this occurs you may have shortness of breath and have fluids build-up in your body. This medication can also cause the lungs to become scarred. If scarring of the lungs occurs it will usually happen three to six months after you receive the medication. Scarring of the lungs can cause death. Cyclophosphamide can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced but you would still be able to have intercourse. Women who are still menstruating may have irregular periods or may no longer have any periods. Whether you are a man or woman, this medication will likely greatly decrease your chances of being able to have a child. It is not known whether the use of cyclophosphamide will cause more side effects or problems with your health in the future.

Etoposide (VP-16): This medication disrupts the growth of cancer cells and destroys them. While taking etoposide you most likely will have diarrhea (loose stools), nausea (feeling sick to

your stomach), vomiting (throwing up), lower white blood cell count that increases your risk of infection, lower platelet count that increases your risk of bleeding, hair loss, stopping of menstrual periods in women, temporary reduced or no sperm production in men. Less likely side effects that you may experience are fatigue, sores in the mouth or on the lips, fever, rash, and loss of appetite. Rare side effects that you may experience are damage to your heart, which may result in a heart attack or heart failure. Your blood pressure may fall during the infusion of etoposide, and etoposide rarely causes numbness and tingling in the fingers and toes, in a condition termed, neuropathy. This may be reversible. Etoposide can rarely cause changes in your liver function.

Total Body Irradiation (TBI): TBI may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), and painful swelling of the saliva gland for a few days. You may also experience short-term hair loss. TBI kills both sick and normal marrow, leading to a lack of red blood cells, white blood cells, and platelets. The short-term loss of these blood cells could cause you to become anemic, develop an infection, and/or bleeding. This will continue until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. There is a risk that cataracts (cloudiness) may develop in your eyes. This may mean partial loss of vision, and you may need contact lenses or surgery to remove the cataracts. The TBI dose used will probably result in sterility (not being able to have children.) It is not known whether the use of TBI will cause more side effects or problems with your health in the future.

The conditioning regimens allowed by this protocol are likely to cause women to enter premature menopause. Men who receive these conditioning regimens are unlikely to be able to father children. However, there is no guarantee that this will happen to you, so you should discuss the need for birth control with your doctor. In any case, you are not protected from sexually transmitted diseases as a result of having these treatments.

Risks Related to the Infusion Peripheral Blood Stem Cells (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can

occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy, irradiation therapy, or both. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines and irradiation cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores you will be given medicine to help control the pain. If your mouth sores are severe you may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy and irradiation therapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy and radiation cause severe lung damage that cannot always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal. A form of kidney failure, called thrombotic microangiopathy may result in reversible or irreversible kidney damage, and may require temporary or permanent dialysis therapy.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. Poor thyroid function can result in fatigue, weight gain, hair loss, depression, dry skin and dry hair; however, this is easily corrected by the medication. As a result of irradiation, cataracts may occur earlier in life compared to a person who had not had a transplant. If you develop cataracts (cloudiness in the eyes) they may require treatment. It is rare, but your kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk you may develop a second cancer as a result of the chemotherapy, irradiation and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

IRB #

Informed Consent to Participate in Research

Study Title: A Phase III Randomized, Multicenter Trial Comparing Sirolimus/Tacrolimus with Tacrolimus/Methotrexate as GVHD Prophylaxis After HLA-Matched, Related Peripheral Blood Stem Cell Transplantation

Principal Investigator Contact Information: (Insert contact information for PI at your site.)

Introduction
We invite you to take part in a research study sponsored by the National Institutes of Health (NIH) and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

First, we want you to know that:

- Taking part in NIH research is entirely voluntary.
- You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.
- You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with your family, friends, or your personal physician or other health professional.

Purpose
During the course of this study, we will attempt to learn about genetic factors that may have an influence on the risks of Graft-vs-Host Disease (GVHD) and long-term outcome after allogeneic stem cell transplantation. GVHD is an immune reaction that occurs after transplantation of stem cells from one individual (the donor) to another (the recipient). GVHD is a form of rejection of the recipient tissues (such as the skin, the intestinal tract and the liver) by the donor immune system. We are interested in studying the small variations or differences in genes, called polymorphisms or variants that could influence the immune system to cause GVHD. At this time, there are several candidate genes that may influence the incidence of GVHD. We would like to store your DNA (which will be isolated from your blood) to eventually study some of these genes. We invite you to participate in this study so that we can learn more about these genetic factors.

Procedures
Sixteen (16) milliliters of blood will be used for the genetic analysis. We ask that you submit a sample of no more than 16 mL, equivalent to three teaspoons. For donors less than 12 years old, a sample of no more than 8 mL, equivalent to 1½ teaspoons, will be requested. If you withdraw from the study, your samples will not be used for other research studies or tested further.

Clinical information (e.g., HLA typing) about you will be collected. The NIH will not have access to the names of the patients enrolled in this study. The clinical information will be coded and compared to the genetic analysis at a later date.

The samples collected for research purposes will be sent to laboratories that have contracts with the BMT CTN to conduct these research tests. They will be labeled with unique codes that do not contain information that could identify you. The link is stored at the Data Coordinating Center for the BMT CTN. The staff at the laboratories where your samples are being tested do not have a link to this code.

In the laboratory, we will isolate DNA from your blood. At a later date, we will test the DNA for the polymorphisms in your genes and in the genes in your stem cell recipient. The polymorphisms will be correlated with clinical outcomes after transplantation.

Your samples will be stored at these laboratories until the entire sample has been used for the research tests or until the end of the study. If any of your samples are leftover after the research studies are completed, these samples will either be destroyed or be sent to the National Heart Lung and Blood Institute (NHLBI) sample repository in Maryland. If your leftover samples are sent to the repository, they will be given an anonymous code. These leftover samples stored at the repository can never be linked to you. Any research performed on these leftover samples must first be approved by an advisory panel at the NHLBI.

If you agree to allow your blood to be kept for research, you are free to change your mind at any time. We ask that you tell [the Principal Investigator] at [address] in writing and let him/her know you are withdrawing your permission for your sample to be used for research. Any unused sample will be destroyed.

Alternatives
You may choose not to participate in this part of the study. The decision to participate in this study will not affect the care given to you by your physicians.

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

At no time will this information be made available to those not directly involved in the study without your written consent. Only the results of the proposed analysis will be collected, presented and published. At no time, will the name or an identifier of patients or stem cell donors be available to anyone except those conducting the study. The investigators who will conduct the genetic analysis will not have access to the names of the patients or donors enrolled in this study. The clinical information will be coded and compared to the genetic analyses to be performed at a later date.

Benefits
It is possible that the information from this study could be important for future transplant donors and recipients. However individual results will not be reported directly to you.

This study will increase our understanding of the factors that influence the risk for developing GVHD after stem cell transplantation. We hope that it will eventually contribute to improvements in prevention and treatment of GVHD. There may be no direct benefit to you or your stem cell recipient from this study. If there are any questions, we will attempt to answer them with the most recent information.

HIPAA[2] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH PURPOSES

1. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Phase III Randomized, Multicenter Trial Comparing Sirolimus/Tacrolimus with Tacrolimus/Methotrexate as GVHD Prophylaxis After HLA-Matched, Related Peripheral Blood Stem Cell Transplantation.*

2. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: Demographic information (e.g., age, date of birth, sex, weight), medical history, physical examination findings, and genetic test results.

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

3. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from (*list hospitals, clinics or providers from which health care information can be requested):*

   _____

   _____

   _____

4. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item 3 and information disclosed by me during the course of the research may be received and used by the following parties:

   - Principal Investigators and the researcher's staff, including Dr. Corey Cutler and Dr. Joseph Antin, Study Chairpersons and staff/laboratories at Dana Farber Cancer Institute
   - National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
   - Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
   - 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 responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

5. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. 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.

7. 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.

8. DNA from your stored blood sample might be used in genome-wide association (GWA) or pharmacogenomics 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 identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease. Pharmacogenomics studies are similar genetic tests but look specifically at genes related to how the body breaks down medications.

   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.

9. 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.

10. This authorization does not have an expiration date.

IRB # _____

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. **Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator at (xxx) xxx-xxxx.

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM BELOW, A or B

A. Adult Patient's Consent.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____
Signature of Adult Patient & Date Signed

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM _____ THROUGH _____.

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable)

_____
Signature of Parent(s)/Guardian & Date Signed

If other than parent, specify relationship: _____

Child's Verbal Assent (if applicable).

The information in the above consent form has been adequately described to my child in language that my child can understand, and my child willingly agrees to participate in the study.

_____
Signature of Parent(s)/Guardian & Date Signed

_____
Signature of Investigator & Date Signed

_____
Signature of Witness & Date Signed