Thomas Jefferson University
Informed Consent Document for Human Subjects Research

Department: Kimmel Cancer Center Blood and Marrow Transplant Program

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Medical Study Title: A Two Step Approach to Allogeneic Hematopoietic Stem Cell Transplantation for High-Risk Hematologic Malignancies Using One Haploidentical Donor

Lay Study Title: A Research Study Using Two-Step Stem Cell Transplant in Patients with High-Risk Diseases of the Bone Marrow

What Is Informed Consent?

You are being asked to take part in a medical research study. As required by federal regulations, this research study has been reviewed and approved by an Institutional Review Board (IRB), a University committee that reviews, approves and monitors research involving humans. Before you can make a knowledgeable decision about whether to participate, you should understand the possible risks and benefits related to this study. This process of learning and thinking about a study before you make a decision is known as *informed consent* and includes:

- Receiving detailed information about this research study;
- Being asked to read, sign and date this consent form, once you understand the study and have decided to participate. If you don't understand something about the study or if you have questions, you should ask for an explanation before signing this form;
- Being given a copy of the signed and dated consent form to keep for your own records.

You should understand that your relationship with the study doctor is different than your relationship with your treating or personal doctor. The treating doctor treats a specific health problem with the goal of improving a medical condition. A study doctor treats all subjects according to a research plan to obtain information about the experimental drug, device or procedure being studied and with the understanding that you may or may not benefit from being in the study. You should ask questions of the study doctor if you want to know more about this.

What is the purpose of this study?

You are about to undergo a hematopoietic stem cell transplant (HSCT) using white blood cells collected from the blood of a partially matched donor in an effort to treat your illness. You are being considered for transplant on this research study because it has been difficult to put your disease into remission or because you have a subtype of the disease that usually relapses even if remission is initially achieved. When a disease is resistant to radiation or chemotherapy or it is associated with a greater relapse rate, it is considered high risk disease and it is very difficult to cure. Allogeneic HSCT (receiving cells from a donor) relies not only on the intensive chemotherapy and radiation that are given during HSCT, but more importantly, on the donor's transplanted cells to fight the disease. This type of therapy is used for high risk patients in an effort to achieve long-term control of the disease. The advantages of using partially matched donors is that their cells may be better at recognizing cancer because they are not completely matched to the patient's cancer cells, and there are usually many more partially matched donors available than completely matched family donors. Patient survival rates using a partially-matched related donor have traditionally been lower than survival rates after matched-sibling transplants. This is because patients receiving transplants from partially matched donors have had higher rates of infection and other complications.

At Jefferson, over 150 patients have undergone partially matched HSCT since 2006. At that time a new way of performing partially matched donor HSCT was developed that uses 2 different steps. This 2 step approach uses chemotherapy and radiation to treat the disease and help the body accept the donor's cells. The chemotherapy and radiation utilized in this treatment have been used safely for decades. What is different in the 2 step approach is that the donor's cells are given in 2 separate steps to allow the partially matched transplant to be performed with fewer complications. We have found the 2 step method to be safer and more successful compared to traditional haploidentical HSCT. Despite many patients achieving long term survival after undergoing HSCT on the 2 Step approach, disease relapse after the HSCT has decreased the success rate of this procedure for some patients. Disease that relapses after HSCT is very hard to treat and often results in death. Most of the patients who relapsed after HSCT on the 2 Step approach had high risk disease. All of these patients achieved remission after transplant for a few months, but their disease was able to escape detection by the donor immune system and it came back. Having high risk disease is a well-known risk factor for relapse after allogeneic transplant.

The purpose of this research study is to try to decrease relapse rates after HSCT in high risk patients being treated on the 2 Step approach. In this research study, a way of strengthening the response of the donor cells against the disease has been developed as will be explained below.

How many individuals will participate in the study and how long will the study last?
We hope to enroll **up to 40** patients at Jefferson. Your involvement in the study will last about 1 year after transplant. The entire study will take about 7 years to complete.

What will I have to do during the study?
Procedures/Treatment
Selection of Donors
You and your eligible family members (parent, child, or sibling) will have blood drawn for white cell typing. This typing is called HLA typing and helps the transplant team determine to what degree your relative matches you if at all. Donors are selected based on the predicted ability of their white cells to fight your disease and the way the different white blood cell types match each other. After selection, your donor must come to Jefferson and have a thorough check-up to make sure they are healthy enough to donate for you. Some of the blood, marrow, and saliva collected from you before HSCT will be stored for analysis after HSCT. After HSCT, we will use these specimens as a comparison to your post HSCT immune system.

The Transplant
You will be admitted to the hospital for the transplant after you have a thorough evaluation to make sure you are healthy enough to undergo the procedure. In the hospital, you will first receive radiation over a period of 3 days to treat your disease and get your body ready to accept the donor's cells. Two days later, you will receive your donor's lymphocytes. Lymphocytes are a type of white cell that helps you fight infection. Your lymphocytes and your donor's will react against each other because they are only partially matched. Therefore after their infusion you will develop a high fever and in some cases, you may also develop a rash and diarrhea. A few patients treated on the first 2 step studies developed low blood pressure as well. No patient treated with this type of transplant at Jefferson had any permanent damage from the infusion of the donor's lymphocytes. Giving you your donor's lymphocytes is the first step of the 2 step transplant process.

Donor's lymphocytes can attack both your cancer cells and the normal tissues of your body as if they were foreign substances. If a donor's cells attack cancer cells, it is called a "graft versus tumor" (GVT) response. If a donor's cells attack normal cells, it is called a "graft versus host" (GVH) response. After your donor's lymphocytes are infused, it is thought that they may be destroying any remaining cancer cells because of a GVT response. However, they may also attack your normal tissues because of a GVH response. Therefore, a few days after they are given to you, the reaction will be stopped by giving you a chemotherapy drug called cyclophosphamide. This drug will work to destroy the active lymphocytes, further treat your disease, and calm down the reaction from the donor lymphocyte infusion.

Two daily doses of cyclophosphamide will be given. You will then have a day of rest. After the day of rest, you will receive your donor's stem cells. The stem cells will help your counts recover and are the second step of this 2 step transplant process.

The transplant schedule is summarized below:

Day -11	Admit to the Bone Marrow Transplant Unit
Days – 10, -9, -8	Total Body Irradiation in the AM and PM
Day -7	Rest
Day -6	Receive the Donor Lymphocyte Infusion in the Afternoon
Days -5 & -4	Rest days (You will be having the reaction to the lymphocytes these days)
Day -3, -2	Receive 1 dose of Cyclophosphamide Each Day
Day -1	Rest; receive Tacrolimus & Mycophenolate Mofetil (MMF)
Day 0	Receive Donor Stem Cells

After Day 0, the hospital admission will last a minimum of 2 to 3 more weeks until your blood counts recover and you are healthy enough to go home.

In the previous 2 step research studies, the same dose of radiation was given over 4 days and the dose of donor lymphocytes was given immediately after the last radiation dose. In this research study, the radiation will be given over 3 days. The 3-day radiation schedule is an alternate one that is used by many other centers that perform HSCT. The radiation days were shortened to add extra time between the last day of radiation and the infusion of the donor lymphocytes. You will receive your donor lymphocytes approximately 48 hours after the last dose of radiation. This schedule change was made so that more time is given for the tumor cells to die from the radiation before your donor's lymphocytes are given. It is hoped that this will make the donor cells more effective and decrease the chances of relapse after HSCT.

After discharge you will continue to be monitored closely. Blood cell count checks, studies that examine immune recovery and testing for viruses are done frequently. Bone marrow examinations will be performed as well. If you experience a fever or other new symptoms, you will be readmitted to the hospital for further evaluation. As an outpatient, you will be monitored very closely for at least the first 12 months after transplant. The official part of this study ends at this time. However, as a post-transplant patient you will be monitored and treated if necessary for the rest of your life.

In the event of relapse, your marrow, blood, and buccal specimens that were collected may be analyzed to assess whether there have been changes in the tumor that may have caused relapse. This information would be used to help guide your doctor in providing your future treatment options and/or be used for future research. Your study doctor will share with you the results of the additional testing.

What are the risks or discomforts involved?

Risks of Allogeneic Transplant

The treatment offered in this study may extend survival. It could also cause complications that could lead to death earlier than death from your existing cancer.

Total Body Irradiation and High-Dose Chemotherapy

- Nausea, vomiting, loss of appetite, weight loss
- Fluid retention causing swelling and/or fluid in the lungs
- Excess weight gain
- Myelosuppression (decrease in white blood cells, red blood cells, platelets), with increased risk of infection, bleeding, and need blood transfusion therapy
- Alopecia (hair loss), dry skin
- Sterility
- Stomatitis (sore mouth, or thick sputum), abdominal cramps, diarrhea, intestinal inflammation
- Watery stools
- Swollen salivary glands, dry mouth
- Skin rash
- Bladder irritation or damage which may produce burning or bleeding on urination
- Central nervous system abnormalities (unsteadiness while walking, injury to the nerves, mood or personality changes, sleepiness, and/or coma)
- Liver damage
- Heart damage
- Kidney damage
- Lung damage, including lung inflammation and scarring
- Cough
- Cataracts (or possibly irreversible vision impairment)
- Increased chance for developing other cancers
- Fatigue, weakness or headache
- Severe allergic reaction leading to facial swelling or throat closure

There is a very rare complication of HSCT called transverse myelitis. This and other neurological conditions are rare side effects but could develop due to nerve damage from the chemotherapy, infection, or your donor's cells. This side effect can decrease the ability to move your limbs normally and requires treatment for months to years or even result in death.

Side Effects Specific to Cyclophosphamide

- Suppressed immune system
- Heart failure, irregular heartbeat, fluid around the heart
- Inflammation and bleeding from the bladder
- Severe allergic reaction leading to facial swelling or throat closure

Marrow Treatment Procedures:

- Slow bone marrow growth or failure of bone marrow to grow at all
- Fever

- Contamination of donor cells causing infection by bacteria or viruses
- Increased risk of lymph gland tumors

Side Effects after the Donor Lymphocyte Infusion

- High Fever
- Diarrhea
- Skin Rash
- Low Blood Pressure
- Life-Threatening Allergic Reaction

Side Effects of Medications used to Prevent GVHD

- Decreased blood counts
- Destruction of red cells or platelets
- Kidney injury
- Neurological changes

After the donor cells are given through your vein, there is a period of time before your blood cell counts recover. During this time, you will be at high-risk for infection and bleeding. Even though you will be monitored closely and treated aggressively for these problems, they may lead to death. After your blood cell counts recover, you may still need to take growth factors and have transfusions if the blood cell counts do not completely recover. You will be at risk for infection for months to years after transplant that can result in death.

Rejection & Graft Versus Host Disease (GVHD)

There is a risk that your body may reject your donor's cells. Your donor cells also may not engraft in you fully, and you may need additional donor cells with or without further chemotherapy to prevent or treat rejection or sluggish blood count recovery. Both of these risks can result in death. There is also a risk of GVHD after transplant which could prove to be fatal. The donor lymphocytes are the major type of cell that can cause GVHD. Signs that you are developing this condition are skin rash, eye and mouth soreness, jaundice, nausea and vomiting, and diarrhea. You will be given immunosuppressive drugs to prevent GVHD from developing. These drugs can suppress your blood cell counts, and cause you to have a higher chance of getting an infection. The majority of donor lymphocytes that you will receive will be given in the first part of the transplant and will be calmed down by cyclophosphamide. However, there is a small amount of lymphocytes that are present in the stem cell product which is given after the cyclophosphamide and therefore will not be calmed down. We will use a special processing method explained below to make sure that the majority of these lymphocytes have been removed. We have not experienced a high lymphocyte amount in any stem cell product since we began using this processing method, however if a higher than desired amount of lymphocytes are present, you will be informed and should be aware that you will be at higher risk for GVHD.

There is no guarantee that you will achieve a permanent cure from this treatment. The transplant may not adequately treat your disease, or you may relapse later.

You will continue to be monitored closely after discharge from the hospital. After transplant, you will have both blood and marrow taken on a regular basis to evaluate your response to the treatment. After discharge, if you develop fever, signs of GVHD or any differences in your normal health, you will be readmitted to the hospital for further evaluation and treatment.

In the 2 Step approach, it is important that your donor's cells are separated and given to you at certain times and at the prescribed doses. The laboratory tool that will be used to process your donor's cells is called the CliniMACS® device. This device is not approved by the United States Food and Drug Administration (FDA) to separate cells in HSCT and is authorized only for research purposes. Therefore, we have obtained an exemption from the FDA to use the CliniMACS® device as part of the transplant process on this research study. This device has been safely used in Europe for many years and many transplant centers in the United States use it with an exemption from the FDA. We believe that this device is more effective in preparing the donor cells for transplant than the older device that we have used in the past.

There are potential risks involved in processing your donor's cells with this device. The donor's cells may be contaminated or spilled when using the device resulting in a poor cell dose and delayed or failed engraftment of donor cells in your marrow. Several safety procedures are built in to the use of the machine to prevent this from happening. A mouse antibody and iron are used in the processing of donor cells using the CliniMACS® device. Small amounts of these substances can get into your bloodstream when you receive your donor's cells. Both of these substances can cause allergic type reactions such as chills, fever, chest pain, vomiting, and swelling. A severe allergic reaction called anaphylaxis could also occur. This reaction can result in death. You will be monitored closely on the transplant unit when you receive your donor's cells and be treated immediately if these reactions develop. The initial patient safety study for CliniMACS® device was performed in Europe. In this study, no side effects were reported with the use of the device. In addition, all donor cell products will be washed prior to you receiving them to remove most or all of these substances.

Risks Specific to This Research Study

In this study, we will be examining whether changing the timing of the donor lymphocyte infusion helps decrease relapse rates after HSCT. There is no guarantee that this change in timing will prevent relapse after HSCT. The change in this timing may have beneficial, deleterious, or have no effect at all on relapse rates after HSCT using the 2 step approach.

You should call the study doctor as soon as possible at 215-955-8874 if, during the course of this study, you develop any of these side effects or symptoms. The study doctor has told you that if your condition worsens, if side effects become very severe, or if it turns out that being in this study is not in your best interest, you will be taken out of the study.

What are the risks to fetuses, infants and pregnant women

Pregnant women or women who are breast feeding should not be in this study because exposure to chemotherapy, radiation and many of the HSCT-related drugs are hazardous to an embryo, fetus or nursing infant. Even medications that are well known and prescribed may have adverse effects on an embryo or fetus. As with any medication, there are unknown risks. To be in this study you and your partner must practice adequate birth control measures. The study doctor will discuss acceptable methods of birth control with you. If you are a woman of childbearing potential, you will have a pregnancy test before making a decision about being in this study. This requires either a urine test or that blood be drawn from a vein in your arm (1-2 tsp.) one or two days prior to the start of the study. The results of this pregnancy test will be made available to you prior to the start of the study.

If you become pregnant during the course of this study, you should notify the study doctor as soon as possible.

If you are a man participating in this study, you also should practice adequate birth control because investigational drugs may have adverse effects on sperm that could also adversely affect a fetus. If your partner becomes pregnant during the course of the study, the sponsor may want to follow her through the pregnancy and receive information on the pregnancy outcome. She will be asked to sign a separate consent form or a form for release of medical information for that.

If you are a person in a same sex relationship, it is not necessary for you to practice birth control. However, if you are female, you will still have to have pregnancy tests according to the study protocol.

Are there alternatives to being in the study?

You do not have to participate in this study. There may be other alternatives that could be considered. These alternatives would include: receiving agents to control your disease and to make you comfortable when your disease progresses. You have the option of undergoing transplant at another center, or at Jefferson using another type of transplant regimen. The study doctor will provide information about the study and any alternative treatments available to you.

How will privacy and confidentiality (identity) be protected?

Federal regulations require that certain information about individuals be kept confidential. This information is called "protected health information" (PHI). PHI includes information that identifies you personally such as name, address and social security number, or any medical or mental health record, or test result, that may have this sort of information on it. The laws state that you see and review your TJU or Thomas Jefferson University Hospital medical records at any time. However, in a research study, you may not see the study results or other data about the study until after the research is completed unless the study doctor decides otherwise.

If you join this study, the following individuals or entities may have access to your PHI and by law must protect it. These include investigators listed on this consent form and other personnel of Thomas Jefferson University, Jefferson University Physicians, and Thomas Jefferson University Hospitals, Inc. involved in this specific study, the University's Division of Human Subjects Protection and the Institutional Review Board (IRB), and your health insurance company (if necessary for billing for standard medical care). It may also be provided to other people or groups as follows:

- the Center for International Blood and Marrow Transplant Research (CIBMTR), an organization that collects data nationally on transplant patients

Your PHI may also be shared with the following entities that, while not obligated by law to protect PHI, will protect it to the best of their ability:

- The Food and Drug Administration (FDA)
- A Data and Safety Monitoring Committee (DSMC),
- Research Monitors hired by the sponsor to oversee the study and review medical records to ensure study-related information is correct,
- With any person or agency required by law.

The following information will be provided to the study sponsor and other entities noted above:

Study data for analysis: Immune system typing information, doses of donor cells used, side effects of transplant, overall survival, relapse, immune system recovery data, medications used, and performance status.

Demographic data: Name, age, sex, occupation, relationship of donors and recipients

Other: Diagnosis and staging information, health status at the time of transplant, previous therapies

If you develop an illness or injury during the course of your participation in this study, other PHI about treating and following the condition may be generated and disclosed as it relates to this study. Your PHI may be used/disclosed indefinitely.

You may quit the study and revoke permission to use and share your PHI at any time by contacting the principal investigator, in writing, at:

Dolores Grosso, DNP, CRNP
925 Chestnut St., Suite 420
Philadelphia, Pa. 19107

If you quit the study further collection of PHI will be stopped, but PHI that has already been collected may still be used.

The results of clinical tests and procedures performed as part of this research may be included in your medical records. The information from this study may be published in scientific journals or presented at scientific meetings but you will not be personally identified in these publications and presentations.

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

What if I am injured as a result of being in this study?
In the event that you experience a research-related injury, necessary and available medical care (including hospitalization) will be provided. A research-related injury is a physical injury or illness resulting to you that is directly caused by any procedure or treatment used in this study that is different from the treatment you would receive if you were not participating in a research study. If you are physically injured due to any drug/substance or procedure properly given under the plan for this study, medical expenses for treating the injury will be billed to your insurance carrier. You should be aware that some costs may not be covered by insurance. There is no plan to provide compensation for loss of wages, lost time from work, personal discomfort, or for injuries or problems related to your underlying medical condition(s).

If you receive a bill related to a research-related injury that seems wrong, please discuss it with the study doctor or research coordinator.

Will I benefit from being in this study?
You may not benefit from being in this research study, but we hope that what we learn may be helpful to future patients or society in general. Possible benefits from being in the study may include less of a chance of relapse and a greater chance of survival after transplant.

Will I be paid for being in this study?
You will not receive payment for your participation in this study.

Will I be told about any new findings?
Anything learned during the study, beneficial or not, that may affect your health or your willingness to continue in the study, will be told to you and explained.

Are there costs related to being in this study?
The investigational methods used in this study will not result in any charges that are in addition to those that are associated with a standard HSCT.

Research Procedures
The investigational device used in this study has been purchased by Thomas Jefferson University. The investigational procedures in this study relate only to the examination of outcomes based on recipient-donor transplant combinations.

Standard Testing Procedures

Procedures, tests and doctor's charges resulting from being in the study, or that may be done while you are in the study, that are considered standard of care will be billed to your health insurance carrier. These are charges that you would have whether or not you were participating in a research study. It is possible that your insurance company may deny payment. If that happens you may be responsible for some or all of these charges. The study doctor will explain to you which procedures, tests and doctor visits are considered standard of care.

If you receive a bill that you think is wrong, please discuss it with the study doctor or research coordinator.

Can I be removed from the study or quit the study?

Your decision to participate in this research study is entirely voluntary. You have been told what being in this study will involve, including the possible risks and benefits.

Your participation in this research project may be terminated by the study doctor without your consent for any reason that he/she feels is appropriate.

You may refuse to participate in this investigation or withdraw consent and quit this study without penalty and without affecting your ability to receive medical care at Thomas Jefferson University.

If you withdraw from this study, you may continue treatment with your Jefferson doctor, or you may seek treatment from another doctor of your choice.

Should you decide to withdraw from the study, please be sure to inform the study doctor. Additional tests or procedures may be needed to ensure your safety. The study doctor will explain why these tests or procedures are necessary.

CONTACT INFORMATION

Telephone number for questions about your rights as a research participant	The Jefferson Institutional Review Board	215-503-8966
For questions, concerns or complaints about the research, or if you suspect a research-related injury	The Principal Investigator, Dolores Grosso, DNP, CRNP or any co-investigator listed at the beginning of this form	215-955-8874
If you have difficulty contacting the study staff	Call the Jefferson Office of Human Research	215-503-0203

If you want more information about the Jefferson Institutional Review Board or Jefferson's Human Research Protection Program, please visit our website at http://www.jefferson.edu/human_research/irb/index.cfm.