Affix Patient Label Here

Masonic Cancer Center, University of Minnesota
Blood and Marrow Transplantation Program

CONSENT TO PARTICIPATE IN RESEARCH

Reduced Intensity Conditioning (RIC) and Transplantation of HLA-Haploidentical Related Hematopoietic Cells (Haplo-HCT) For Patients With Hematologic Malignancies

Principal Investigator: Mark Juckett, MD

You are being considered for a bone marrow transplant and you do not have a suitable matched donor in the traditional sense. This is the case for approximately 60% of persons in need of a transplant. An alternative is to use a close relative (sibling, parent or child) that is “half-matched” (haploidentical) as the donor. Using haploidentical donors greatly increases the number of potential donors allowing more persons to undergo a potentially curative bone marrow transplant.

This treatment plan is also using a reduced intensity conditioning (RIC - a short course of chemotherapy with or without radiation therapy) to prepare the patient for the transplant. With a traditional bone marrow transplant, high doses of chemotherapy with or without total body irradiation (TBI) are given before the donor cells are infused (transplanted) to 1) make room in the bone marrow for the donor cells to grow and 2) wipe-out the patient’s immune system to reduce the chance of rejection. The traditional treatment approach has severe side effects associated and a long recovery time limiting it use to younger people and people free of other health issues. With RIC, the side effects are less severe and blood counts recover sooner reducing the risks of transplant related complications, such as infection.

This form is called a consent form. The intent of this form is to let you know the purpose of this study, the treatment plan, and the possible risks and benefits of having a transplant using a haploidentical donor and a reduced intensity conditioning. If you wish to take part in this study, you will be asked to sign this consent form.

This research study is being conducted at the Masonic Cancer Center of the University of Minnesota. Mark Juckett, MD is the principal investigator (the physician in charge) of this research study.

Study Purpose

The primary purpose of this study is to determine the cancer free survival at 1 year after transplant with a reduced intensity conditioning transplant for the treatment of a hematologic malignancy (cancer of the blood) using a haploidentical donor as the source of the bone marrow cells. This is done by reviewing standard medical information collected on all transplants. The results of this study will be compared with historical information on transplants using other donor sources and/or pre-transplant preparative regimens.

Up to 84 patients, 75 years of age or younger, will be enrolled in this study.

Study Procedures

Many of the procedures on this study, such as the donor collection and the post-transplant graft-versus-host disease preventive drugs, are considered clinical care. The goal of clinical care is to help you get better or to improve your quality of life. Doctors can make changes to your clinical care plan as needed.

Pre-Transplant Work-Up

The following routine tests and evaluations may be done to determine eligibility for a transplant:

- medical history
- physical exam including vital signs, height and weight
- consultation with radiation therapy and other specialists as needed
- routine blood tests (requiring approximately 3 tablespoons of blood) to evaluate bone marrow, liver, and kidney function, other disease related testing, and if not previously HLA typing for determining a suitable donor
- urinalysis
- a pre-transplant viral panel (requiring 1 tablespoon of blood) to check for exposure to viruses, including hepatitis and HIV. Persons with active hepatitis are not eligible for transplant under this study. It will be recommended that a Blood Bank physician contact a personal physician regarding further testing. By law, the Minnesota Department of Health must be notified of persons testing positive for hepatitis or HIV.
- pregnancy test for females of child bearing potential

- an electrocardiogram (ECG) - a test that shows the electrical activity of the heart
- an echocardiogram or MUGA scan - a test that shows the pumping ability of the heart - this may be skipped if done in the previous 1 month
- pulmonary function test (PFT) - a breathing test that tells how your lungs are working (measures the amount of air taken into the lungs and exhaled as while breathing)
- bone marrow biopsy and aspirate - a procedure to remove soft tissue (biopsy) and the liquid (aspirate) from the hollow part (bone marrow) of a bone, usually the hip

If you are found to be healthy enough for a transplant and agree to undergo a transplant, a central venous catheter will be placed in a large vein in the chest area to allow easier administration of intravenous (IV) medications and for collecting blood without additional needle sticks. In most patients, the catheter can remain in place for the duration of the treatment.

Transplant Procedures

Treatment will be given in 3 components – 1) the preparative chemotherapy given over several days followed by 2) the hematopoietic stem cell infusion (transplant) and 3) two additional doses of cyclophosphamide plus medications to reduce or prevent some of the risks of the transplant procedure.

Treatment Summary

Day	Drug or Procedure	Dose Information
-6, -5, -4, -3, -2	Fludarabine	1 daily dose over 30-60 minutes (5 doses total)
-6	Cyclophosphamide	1 daily dose over 1 to 2 hours
-5	Melphalan	1 daily dose over 15-20 minutes (if you are 55 years or older and/or have other health problems – the dose of melphalan will be either removed or reduced by about 1/3 to increase safety)
-2, -1	Total body irradiation (TBI)	
0	Donor stem cells (transplant) infused over less than 1 hour	
+3, +4	Cyclophosphamide	1 daily dose over 1 to 2 hours (2 doses total)
+5	Begin tacrolimus (or sirolimus), mycophenolate mofetil (MMF) to prevent rejection and G-CSF to help blood counts recovery	

Note about treatment day numbering with transplants: The day of the transplant is called day 0. Days before the transplant are indicated by a negative number and days after the transplant are indicated by a positive number (or no sign). This treatment begins on day -6 or 6 days before the day of the planned transplant.

On the morning of the transplant (day 0), bone marrow or peripheral blood stem cells will be collected from your donor.

Follow-up and Care After the Transplant

Frequent physical exams and blood tests will be done to check for blood count recovery and to look for side effects. During the first 2-3 weeks after the transplant, up to 2 tablespoons of blood will be drawn daily. Appropriate supportive care is given to all patients after a transplant. This may include transfusions of red blood cells or platelets, antibiotics to prevent or treat infections and drugs to encourage bone marrow recovery.

Blood will be drawn less frequently as blood counts improve. After blood count recovery and discharge from the hospital, at least weekly follow-up visits in the outpatient clinic will occur for the 1st 3 months after the transplant.

Routine clinic follow-up is required at 6, 12 and 24 months after the transplant with at least yearly contact (in person, by phone or mail) after that.

Risks of Treatment

The drugs used before and after the transplant will result in side effects. There are also risks associated with the transplant procedure. There is a risk of having all, some, or none of these side effects and the side effects may vary in severity. The severity may be mild, moderate or severe, including death. Any symptoms or conditions that are present before treatment starts may get worse. Also, there is always the chance of a side effect that is not yet known.

Medications are given to prevent or lessen the side effects. Many side effects are reversible and go away shortly after the treatment is completed, but in some cases side effects can be serious, long-lasting, or even fatal.

Risks Associated with the Pre-Transplant Conditioning:

Fludarabine		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness • diarrhea • loss of appetite • tiredness (fatigue) • nausea • vomiting • fever and chills • infection	• pneumonia • diarrhea • loss of appetite • weakness • pain	• numbness and tingling in hands and/or feet related to irritation of nerves • changes in vision • agitation • confusion • clumsiness • seizures • coma • cough • trouble breathing • intestinal bleeding • weakness • death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes

Cyclophosphamide		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• low white blood cell count with increased risk of infection • hair loss or thinning, including face and body hair (usually grows back after treatment) • nausea • vomiting • loss of appetite • sores in mouth or on lips • bleeding from bladder, with blood in urine • diarrhea • long-term or short-term infertility (inability to have children) in women and men	• low platelet count (mild) with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if pregnancy occurs while taking cyclophosphamide	• heart problems with high doses, with chest pain, shortness of breath, or swollen feet • severe allergic reactions • skin rash • scarring of bladder • kidney damage (renal tubular necrosis) which can lead to kidney failure • heart damage, with trouble getting your breath, swelling of feet, rapid weight gain • scarring of lung tissue, with cough and shortness of breath • second cancer, which can happen years after taking this drug

Cyclophosphamide		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
		• death from infection, bleeding, heart failure, allergic reaction, or other causes

A drug called Mesna will be given to reduce the risk of damage to the bladder (hemorrhagic cystitis). The most common risks of Mesna include: nausea, vomiting, tiredness, headache, pains in your legs and arms and an unpleasant taste in your mouth.

Melphalan		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• nausea (at higher doses) • vomiting (at higher doses) • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • anemia (low red blood cell count) with symptoms like tiredness, paleness, or trouble catching breath	• short-term or long-term infertility (inability to have children) • weakness	• severe allergic reaction • loss of appetite • scarring (fibrosis) or inflammation of lungs • hair loss, including face and body hair • rash • itching • second type of cancer (may happen years after treatment) • death from lung damage or other causes

Total Body Irradiation		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• nausea and vomiting • diarrhea • cataracts • sterility (inability to have children) • endocrinopathies (hormone imbalance due to damage to the endocrine gland) • stunned growth in children • intestinal cramps • mucositis (mouth sores)	• parotitis (swelling and inflammation of the parotid gland) • interstitial pneumonitis (explained below in the damage to vital organs section) • generalized mild reddening of the skin • veno-occlusive disease (VOD - explained below in the damage to vital organs section)	• dysphagia (difficulty swallowing) • deformities of the backbone (vertebrae) • nephropathy (numbness or tingling in hands and/or feet) • risk of 2nd malignancy years later (when given along with chemotherapy)

Risks Associated with Transplant:

Risk of Radiation

As part of this study you may undergo a chest CT to look for infection in your lungs prior to transplant. This procedure involves exposure to ionizing radiation. The average amount of radiation that the average person would receive from this procedure is approximately three times that received from natural sources of radiation by a Minnesota resident in one year (3 mSv). This exposure involves minimal risk and is necessary to obtain the research information desired from participation in this study.

Donor Cell Infusion Reaction: The donor cells are given in a manner similar to a blood transfusion, and as with a blood infusion there is a small risk of an allergic reaction to the cells as they are given. This may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, and headache. Medications are given before the cell infusion to reduce the risk of an allergic reaction. If during the infusion symptoms develop, the rate of the infusion may be slowed or stopped and/or additional medications given to reduce the intensity of any reactions.

Graft versus Host Disease: (also called GVHD) is caused by donor (or graft) cells attacking the patient's (recipient or host) body. GVHD can occur either within the first 3 months after the transplant (acute GVHD) or later, usually around 6 to 8 months after the transplant (chronic GVHD). Drugs (two additional doses of cyclophosphamide, plus tacrolimus (or sirolimus) and MMF) are given after the transplant to suppress the immune system reducing the risk of and/or severity of GVHD. If GVHD occurs, standard GVHD therapy is given.

Acute GVHD commonly involves the skin, liver, and the intestines with symptoms such as a skin rash, jaundice (yellowing of the skin), nausea, vomiting and diarrhea. The treatment of acute GVHD may require high doses of cortisone-like drugs (methylprednisolone or prednisone)

Chronic GVHD usually involves the skin, liver, eyes, glands and joints with symptoms such as skin rash, jaundice (yellowing of the skin), dry mouth or/eyes, weakness or a pain and tightening around the joints. Chronic GVHD may be mild and respond to drugs which suppress the immune system, or it could be very severe; it may also last for several years.

You will be given drugs to reduce the risks of GVHD. You can read more about the risks of these drugs in the Appendix of this document.

Marrow Aplasia (Suppression of the Bone Marrow): All patients will have low blood counts from the chemotherapy, but are expected to normalize within a few weeks after the transplant. A drug called filgrastim (G-CSF) will be given beginning on day +5 to help speed the recovery of the blood counts.

filgrastim (G-CSF)		
Common	**Less Common**	**Rare, but may be serious**
• bone or muscle pain • increased levels of liver enzymes and uric acid in the blood • headache • tiredness	• injection site reaction (redness, pain, or swelling) • nausea	• allergic reaction • spleen enlargement or rupture – symptoms of an enlarged spleen include a feeling discomfort, fullness, or pain on the upper left side of the abdomen; this pain may spread to the left shoulder • serious lung problems (ARDS) • worsening of skin rashes

Marrow aplasia and failure to engraft are names used to describe when blood counts do not recover as expected.

Symptoms of marrow aplasia include increased risk of bleeding and/or bruising due to low platelets, increased risk of infection due to low white blood cell count, and shortness of breath and tiredness as a result of anemia due to low red blood cell count. Marrow aplasia is treated with blood transfusions and growth factor (which stimulates bone marrow cells), and other precautions. Severe or prolonged aplasia (lasting more than 1 month) can lead to death, usually from infection. If the bone marrow does not recover, sometimes it can be corrected by another stem cell transplant; however not all patients are able to have a transplant.

Damage to the Vital Organs: Some patients will experience severe lung problems due to infections such as cyomegalovirus (CMV) and/or a reaction of the lungs to the chemotherapy. Although treatments are available for this type of pneumonia, interstitial pneumonia can be fatal.

Some patients will suffer veno-occlusive disease of the liver (VOD), a complication that may result from high doses of chemotherapy and/or radiation. Patients who have VOD

become jaundiced (yellowish skin), have liver function abnormalities, abdominal swelling, and abdominal pain. Although many patients recover, these complications may result in organ failure and permanent damage, or even death.

Serious Infections: Complete recovery of the immune system may take many months following the initial recovery of the white cell count. During this time, there is an increased risk of infections. Medications to reduce the risk of developing an infection are prescribed during this time; however, preventative treatments are not always effective. If an infection develops, discharge from the hospital may be delayed or re-hospitalization required. Infections can be fatal.

Sterility and Future Childbearing Potential for Men and Women: Chemotherapy may affect fertility. Male patients may become sterile (unable to produce sperm). Female patients may find that their menstrual cycle becomes irregular or stops permanently. Damage to reproductive tissue may result in birth defects or permanent inability to father a child or become pregnant. These risks and options will be discussed in detail with the medical staff before beginning treatment. However, PREGANCY CAN OCCUR, and an effective method of birth control must be used by sexually active men and women.

Risk to the Unborn: The treatments are NOT safe at any stage of pregnancy. Therefore, pregnant and nursing women are not eligible for this treatment. Women who have the potential of becoming pregnant must use some form of effective birth control.

Risks of Using a Haploidentical Donor

Based on previous experience at this instutition and others there is lower transplant related mortality (TRM), a greater chance of disease relapse but similar overall survival when compared with other transplants using a related or unrelated matched donor.

Benefits of Study Participation

If you agree to take part in this study, there may or may not be direct medical benefit to you. It is hoped the information learned from this study will benefit other patients that may be treated with a haploidentical bone marrow transplant using a reduced intensity conditioning in the future.

Alternatives to Study Participation

You may choose to not participate in this study. Other treatments that could be considered for your condition may include:

- a standard of care transplant using the most medically appropriate pre-transplant regimen and/or source of donor cells
- treatment with other drugs or combination of drugs
- other investigational treatments at this institution or at other research centers
- comfort care only, where treatment is directed only at reducing symptoms, relieving suffering, and maximizing comfort, dignity, and control. In comfort care only, treatment is not directed at curing, slowing, or reversing your disease.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Study Costs

Costs associated with treatment and care will be billed to you and/or your health insurance/health plan in the usual way. Prior to transplant, the Transplant Coordinator will verify your coverage with your insurance company to be sure that you are pre-authorized before beginning any part of this study. If you have concerns or questions regarding coverage or potential charges, you should contact the patient financial representative at (612) 273-2800.

You will receive no payment or compensation for taking part in this study.

In the event that this treatment 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 you or your insurance company. If you think that you have suffered a treatment related injury let the study physicians know right away.

Confidentiality

The records of this study will be kept private. Information will be kept in your electronic medical record, paper research chart, and in study data forms. Information gained from this study will be used for research and educational purposes. If information from this

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

In addition, transplant related clinical information is routinely collected and stored in the University Of Minnesota Transplant, Biology and Therapy (TBT) Database to fulfill reporting requirements to organization such as the Center for International Blood and Marrow Transplant Research (ICBMTR).

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Departments at the University of Minnesota with appropriate regulatory oversight
- The Masonic Cancer Center at the University of Minnesota and/or their designee
- The National Cancer Institute (NCI) and other government agencies involved in keeping research safe for people
- Center for International Blood and Marrow Transplant Research (ICBMTR)

To this extent, confidentiality is not absolute.

A description of this clinical trial is available on 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 may search this web site at any time.

Protected Health Information (PHI)

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Participation

Taking part in this study is your choice. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. You can still get your medical care from this institution.

If you decide to take part in this study, you may leave the study at any time. Once the preparative regimen is started, you may withdraw from continued data collection, however not giving the donor cells could result in your death.

Please let your doctors know if you are thinking about stopping the study so they can discontinue collecting study data. The doctors will discuss with you the available standard options for restoring your bone marrow. The data collected on you prior to withdrawal will remain part of the study database and may not be removed..

Contacts and Questions

The physicians involved in your care are available to answer any questions you may have concerning this study at any time. The study's principal investigator, Dr. Mark Juckett may be reached at (612) 625-8942.

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your child's research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your child's rights as a research participant.
- You want to get information or provide input about this research.

Signature

I have read this consent form or it has been read to me. I have had my questions answered. I agree to take part in this study.

_____ _____

Printed Name of subject Date

_____ _____

Signature of Subject (if no Legally Authorized Representative is used) Date

OR

_____ _____

Signature of Legally Authorized Representative Date

_____

Authority of Subject's Legally Authorized Representative or Relationship to Subject

_____ _____

Printed Name of person obtaining consent Date

_____ _____

Signature of person obtaining consent Date

Signature Block for Witness:
WITNESS STATEMENT:
The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is illiterate
☐ The participant is visually impaired
☐ The participant is physically unable to sign the consent form. Please describe:

_____

☐ Other *(please specify)*:

_____

For the Consent of Non-English Speaking Participants when an Interpreter is Used:
A**s** someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

_____ _____
Signature of Interpreter Date

_____
Printed Name of Interpreter

OR:

Statement from a Non-Interpreter:
As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

_____ _____
Signature of Individual Date

_____
Printed Name of Individual

Appendix - Risks associated with the drugs given to reduce the risk of GVHD:

Tacrolimus		
Common	**Less Common**	**Rare, but may be serious**
▪ kidney problems ▪ loss of magnesium, calcium, potassium ▪ high blood pressure ▪ tremors ▪ increases in cholesterol and triglyceride	▪ nausea ▪ vomiting ▪ liver problems ▪ changes in how clearly one can think ▪ insomnia ▪ unwanted hair growth ▪ confusion	▪ seizures ▪ changes in vision ▪ dizziness ▪ red blood cell destruction

It is very important that grapefruit or drinks with grapefruit juice are NOT consumed while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs**.** Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

In some Tacrolimus may be replaced with Sirolimus – you will be told if this is the case.

Sirolimus (Rapamycin)
• fast heart rate
• pain when breathing, feeling short of breath
• chest pain, feeling weak or tired
• coughing up blood or mucus
• feeling like may pass out
• pale skin, easy bruising or bleeding, weakness
• fever, chills, body aches, flu symptoms
• night sweats, weight loss
• swelling of face, stomach, hands or feet
• rapid weight gain
• pain or burning when urinating
• slow healing of a wound
• joint pain
• nausea, vomiting, diarrhea, constipation, stomach pain
• headache
• acne or skin rash
• high triglycerides and cholesterol

Mycophenolate mofetil (MMF)		
Common	**Less Common**	**Rare, but may be serious**
• miscarriage • birth defects • diarrhea • damage to unborn baby • limited effectiveness of birth control • stomach pain • upset stomach • vomiting • headache • tremors • low white blood cell count with increased risk of infection • increased blood cholesterols • swelling of the hands, feet, ankles or lower legs	• anemia • rash • difficulty falling asleep or staying asleep • dizziness • uncontrollable hand shakes	• difficulty breathing • unusual bruising • fast heartbeat • excessive tiredness • weakness • blood in stool • bloody vomit • change in vision • secondary cancers, such as lymphoproliferative disease or lymphoma • Progressive Multifocal Leukoencephalopathy – a very rare, but serious and often fatal inflammation of the brain

For Females taking MMF:

1. MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.

2. MMF can limit the effectiveness of birth control pills and thus increase your chances of becoming pregnant while taking it.