Blood and Marrow Transplantation Program
Masonic Cancer Center
University of Minnesota

CONSENT TO PARTICIPATE IN RESEARCH

Haploidentical Donor T-cell Replete Allogeneic Hematopoietic Cell Transplant following Reducing Intensity Conditioning for Patients with Selected High Risk Non-Malignant Disease

Principal Investigator: Christen Ebens, MD

For questions about research appointments, the research study, research results, or other concerns, call the study team at: **Principal Investigator:** Christen Ebens, MD Department: Department of Pediatrics **Phone Number:** 612-626-8094 **Email Address:** ebens012@umn.edu	**If you need emergency care:** • Call 911 or go to your nearest emergency room right away. **If you do NOT need emergency care:** • Call or go to your regular doctor. It is important that you tell your regular doctor that you are participating in a research study. If possible, take a copy of this consent form with you when you go.

What is research?

Doctors and researchers are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Researchers learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.
- The goal of treatment is to help you get better or to improve your quality of life. Doctors can make changes to your treatment plan as needed.

What you should know about research studies:

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.

- You can ask all the questions you want before you decide.

What this study is about:

You have a high-risk non-malignant disease and you are considering a hematopoietic cell transplant (HCT) as a way to treat the condition. 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 donor that is "half-matched" (haploidentical) to the recipient. Haploidentical donors may be related to the recipient, such as a sibling or parent, or unrelated donors found through a donor program, such as BeTheMatch. Using haploidentical donors greatly increases the number of potential donors allowing more persons to undergo a bone marrow transplant.

This treatment plan uses a reduced intensity conditioning (RIC - a short course of chemotherapy with low dose 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.

Study Purpose

Although transplant is standard treatment for your disease, the use of a haploidentical donor combined with RIC conditioning is a newer approach. We are studying how well your cell counts recover by six weeks after the transplant. We are also looking at survival at 1 year after transplant. This is done by reviewing standard medical information collected on all transplants done in the past. The results of this study will be compared with historical information on transplants using other donor sources and/or pre-transplant preparative regimens.

How long will the research last?

We expect that you will be in this research study for two years. After two years, we will ask you to consent to us following your health for the rest of your life.

How many people will be studied?

Up to 20 patients, 55 years of age or younger, will be enrolled in this study.

Study Procedures

Pre-Treatment Evaluation

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

- medical history, including review of disease symptoms
- physical exam including vital signs, height and weight
- consultation with other specialists as needed
- routine blood tests (requiring approximately 3 tablespoons of blood) to evaluate bone marrow, liver, and kidney function and other disease related testing
- If you are a female and menstruating a pregnancy test will be performed.
- urinalysis
- a pre-transplant viral panel (requiring 1 tablespoon of blood) to check for exposure to viruses, including hepatitis and HIV. Persons who test positive for HIV will not be eligible for a transplant. 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.
- human leukocyte antigen (HLA) typing to provide match information for selecting a donor
- an electrocardiogram (EKG) - a test that shows the electrical activity of the heart
- an echocardiogram or multigated acquisition (MUGA) scan - a test that shows the pumping ability of the heart
- any other tests or evaluations as felt medically appropriate

A central venous catheter will be placed in a large vein in the chest area to allow easier administration of intravenous (IV) medications including the above drugs and for collecting blood without additional needle sticks. The catheter will also be used for blood transfusions (if needed) and for infusion of the stem cells (transplant).

Bone Marrow Harvest – The first five patients, and patients that doctors feel may be at higher risk of the transplanted cells not growing in the marrow (graft failure), will have stem cells collected, either by a bone marrow harvest or via peripheral stem cell collection. Cells will be collected during this harvest and saved as a back-up, in case you need a stem cell “rescue” in the event of graft failure. If, after two years, you do not need the harvested cells, they will be discarded, or, with your permission, saved for future research. You will have an opportunity to opt in or opt out of saving your marrow at the end of this consent.

Treatment Plan

Treatment can be thought of in 3 components:

1. therapy to prepare the body for transplant, given over several days using the standard drugs Anti-thymocyte globulin (ATG), Thiotepa, Cytoxan and fludarabine, and radiation (TBI)
2. the transplant on day 0 as an infusion of the donor blood stem cells through the catheter,
3. the recovery phase, including supportive care drugs – sirolimus, mycophenolate mofetil (MMF), and Granulocyte-colony stimulating factor (G-CSF or GCSF)-, both in and out of the hospital.

Day	Drug or Procedure	
Conditioning Regimen		
-9, -8, -7, -6*	ATG	Infused in your IV over 6 hours
-7	Thiotepa	Infused two times in your IV over 2 hours
-6, -5	Cytoxan	Infused in your IV over 2 hours
-6, -5, -4, -3, -2	Fludarabine	Infused in your IV over 1 hour
-1	Radiation**	One time
Transplant		
0	Donor bone marrow cell (transplant)	Infused over less than 1 hour in your catheter
Post Transplant Drugs		
+3, +4	cyclophosphamide	1 daily dose in your catheter
+5	Begin sirolimus	2 or 3 (depending on your body weight) daily doses in your catheter
+5	Begin MMF	3 daily dose in your catheter or as a pill if you are able to swallow pills
Supportive Care		
+5	Begin G-CSF to help blood counts recover	Infused in your IV

*The number of doses of ATG will depend on your body weight and blood count. You will have a blood draw the day before or morning of the first dose of ATG to determine the number of days you will receive the ATG.

**Female patients may elect to have a minor surgery to protect their ovaries from radiation. Please see Appendix 5 for more information

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).

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, medicines 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. Disease specific testing will be done at each visit.

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

Research Blood Sample

We will collect blood (less than 1 tablespoon) for ATG pharmacokinetic (PK) testing. PK testing measures how much drug remains in your system. These research tests will help determine whether ATG is still present in your blood. Having this information will help understand the way you recover after the transplant. The blood sample will be taken on day -1 (the day before your transplant).

Risks of Treatment

There are 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 Preparative Regimen:

Please refer to the attached Appendix 1, labelled “Risks Associated with the Pre-Transplant Preparative Regimen.”

Risks Associated with Transplant:

Stem 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 (GVHD): is caused by donor (or graft) cells attacking the patient's (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 that suppress the immune system are routinely given after a transplant to reduce the risk 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.

As part of standard transplant care, drugs are given to prevent or reduce the severity of GVHD.

Please refer to the attached Appendix 2, labelled "Risks of Supportive Care Treatment" for the risks associated with GVHD preventative drugs.

Marrow Aplasia (Empty Bone Marrow): All patients will have low blood counts from the chemotherapy, but are expected to normalize within a few weeks after the transplant. 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 (G-CSF - which stimulates bone marrow cells), and other precautions, such as an initial bone marrow harvest. 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 transplant; however not all patients are able to have a transplant.

G-CSF will be given as a once a day infusion beginning on day +5 and continuing for 3 days after blood count recovery.

Please refer to the attached Appendix 2 "Risks of Supportive Care Treatment" for the risks associated with supportive care drugs.

Damage to the Vital Organs: Some patients will experience severe lung problems due to 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 the chemotherapy. Patients who have VOD may become jaundiced (yellowish skin), develop liver function abnormalities, abdominal pain and weight gain. Although many patients recover, these complications may result in organ failure and permanent damage, or even death.

In order to help the liver and gall bladder the drug ursodiol will be given for at least 30 days after the transplant. It can only be given orally, and potential side effects of ursodiol are generally gastrointestinal (diarrhea, constipation, upset stomach, indigestion, vomiting). Rarely flu-like symptoms can occur.

Serious Infections: Complete recovery of the immune system may take many months. 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.

Incomplete Donor Engraftment: This occurs when an insufficient number of the donor cells are present in the blood of the patient. Your donor may be asked to permit another cell collection to help improve the mix of donor and patient blood and marrow cells.

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.

Sterility and Future Childbearing Potential for Males and Females: Chemotherapy and irradiation 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.

For cALD Patients Only

Anti-Oxidant And Anti-Inflammatory (AO/AI) Supportive Care

ALD patients routinely receive anti-oxidant and anti-inflammatory (AO/AI) supportive care during the transplant and recovery. This is to help prevent disease progression. You will receive a regimen of N-acetylcysteine ("NAC"), celecoxib, vitamin E, alpha lipoic acid starting on day -9 and continuing through day +100.

Please refer to the attached Appendix 3, labelled "For cALD Patients Only," **for risks associated with this supportive care.**

For Hemoglobinopathy Patients Only

Supportive Care

Hemoglobinopathy patients routinely receive Hydroxyurea supportive care. This is to help prevent disease progression. You will receive, or if you are already receiving, continue to receive hydroxyurea for at least one month prior to your hospital admission.

Please refer to the attached Appendix 4, labelled "For Hemoglobinopathy Patients Only," **for risks associated with this supportive care.**

Alternatives to Study Participation

You may decide to not participate in this transplant study. Alternatives include:

- a transplant using a different pre-transplant regimen and/or a different 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 doctors can tell you more about the possible benefits of a transplant and of other options.

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 by learning more haploidentical transplant.

Study Costs

You and your insurance provider will be responsible for all costs associated with the transplant, including the costs of the donor cells, routine diagnostic tests, the preparative regimen, hospitalizations and follow-up clinic visits. You will be responsible for payment of all fees and charges related to medical services not covered and of any deductibles and co-payments. Research funds will cover the cost of the ATG level testing. 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 monetary compensation for your participation in this study.

Research-related Injury:

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 you or your insurance company. If you think that you have suffered a research 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 medical record and in study case report 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.

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

- The University of Minnesota Institutional Review Board (IRB), a group of people who review the research study to protect your rights
- The Masonic Cancer Center at the University of Minnesota and/or their designee
- National and international transplant registries including the Center for International Blood and Marrow Transplant Research (CIBMTR) and National Marrow Donor Program (NMDP)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

To this extent, confidentiality is not absolute.

If you decide to participate in this study, some private health information about you will be stored in a computer database at the University of Minnesota Masonic Cancer Center. This information will include your name and medical record number, date of birth, diagnosis, race/ethnicity, and information about participation in this study. The purpose of storing this information is to assist the Cancer Center in creating reports about research and in making sure that research studies are being done correctly. Your information will not be used for any other purpose. There are no plans to erase information from the database. It will be stored indefinitely at the Masonic Cancer Center.

Monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access.

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 can search this web site at any time.

Research Blood Specimen

Your blood specimen will be sent to Utretch University in the Netherlands for analysis. The sample will only be labelled with the date it was drawn and a unique patient ID number. Samples will never be sent out with any information that can identify you.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Voluntary Participation

You 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; however once the preparative regimen is started, not giving the donor cells could result in your death. Please let your doctors know if you are thinking about stopping the study so it can be done safely.

The study doctor may stop you from taking part in this study if he/she believes it is in your best interest.

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.

New Information

You will be told about new information or changes in the study that may affect your health or your willingness to continue in the study.

Contacts and Questions

The physicians involved in your care are available to answer any questions you may have concerning this study. In addition, you are encouraged to ask questions concerning this study that you may have in the future. If you have any questions concerning this particular study, you may contact the principal investigator of the study, Dr. Christen Ebens at (612) 626-8094.

Whom do I contact if I have questions, concerns or feedback about my experience?

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 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.

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Feedback

After the study, you might be asked to complete a survey about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey after the study is over, but you would like to share feedback, please contact the study team or the Human Research Protection Program (HRPP). "See the "Investigator Contact Information" of this form for study team contact information and "Contacts and Questions" of this form for HRPP contact information.

Autologous Marrow for Future Research

With your permission, your bone marrow left over after two years post-transplant may be stored and used for future research purposes that have not yet been determined. In the event the marrow is used in future research, it will be relabeled in an anonymous manner, so that you cannot be identified in any way. The scientific, diagnostic and/or medical significance of the research to be done is not known. Therefore, neither you nor your doctors will be informed of your individual results, and they will not affect your treatment in any way. Some of this research may result in new inventions or discoveries that may be of potential commercial value and may be patented and licensed for the development of new products. Specimen donors do not retain any property rights to the materials. Therefore, you would not share in any money or other benefits that any entity might receive for these inventions or discoveries. Your decision not to allow storage or future use of your marrow will not affect your ability to participate in this study. If you agree to allow you marrow to be used for future research, you can change your mind later. Please initial below if you agree to have leftover marrow be stored for future research:

I agree to have my marrow stored for future research:

☐ Yes ☐ No *Initials*: _____

If you choose to participate, you will be given a signed copy of this form to keep for your records.

Signatures
Your signature documents your permission to take part in this research.

_____
Printed Name of Patient

_____ _____
Signature of Subject or Individual Legally Authorized to consent for the subject to participate — Date

_____
Printed Name of Subject or Individual Legally Authorized to consent for the subject to participate

_____ _____
Signature of Person Obtaining Consent — Date

_____
Printed Name of Person Obtaining Consent

☐Check if this section is not applicable (no witness used—required for consent of non-English speaking subjects or subjects who do not read English)

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

☐ The participant is unable to read the information

☐ The participant is visually impaired

☐ The participant is non-English speaking

☐ 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 1

Risks Associated with the Pre-Transplant Preparative Regimen:

Anti-Thymocyte Globulin (ATG)		
Common	**Less Common**	**Rare, but may be serious**
• fever • chills • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • pain • headache • abdominal pain • diarrhea • high blood pressure (hypertension) • nausea • swelling of hands and/or feet (peripheral edema) • shortness of breath (dyspnea) • loss or lack of strength (asthenia) • high levels of potassium in the blood (hyperkalemia) • rapid heartbeat (tachycardia)	• feeling poorly (malaise) • dizziness	• severe allergic reaction (anaphylaxis)

Thiotepa		
Common	**Less Common**	**Rare, but may be serious**
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • nausea • vomiting • loss of appetite • temporary or permanent sterility (inability to have	• tiredness (fatigue) • anemia (low red blood cell count) • dizziness • headache • fever • pain where the drug was injected • hair loss, thinning or brittle hair	• blurred vision • confusion • allergic reaction with itching, hives (welts), swelling in throat, wheezing, dizziness, or shortness of breath • second type of cancer • death from infection, bleeding, or other cause

Thiotepa		
Common	**Less Common**	**Rare, but may be serious**
children)	(including hair on the face or body)	

Cyclophosphamide		
Common	**Less Common**	**Rare, but may be serious**
• 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 • death from infection, bleeding, heart failure, allergic reaction, or other causes

Fludarabine		
Common	**Less Common**	**Rare**
• 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	• 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

Fludarabine		
Common	**Less Common**	**Rare**
weakness • tiredness (fatigue) • nausea • vomiting • fever and chills • infection		• 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

Total Body Irradiation		
Common	**Less Common**	**Rare**
• 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 (kidney damage or disease) • risk of 2nd malignancy years later (when given along with chemotherapy)

Appendix 2

Risks of Supportive Care Treatment

Risks Associated with the Graft vs Host Disease (GVHD) Prevention Drugs:

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 Mofetile (MMF)	
Common	**Rare, but may be serious**
• constipation • stomach pain or swelling • nausea • vomiting • difficulty falling asleep or staying asleep • pain, especially in the back, muscles, or joints • uncontrollable shaking of a part of the body • headache • rash	• diarrhea • swelling of the hands, arms, feet, ankles, or lower legs • difficulty breathing • chest pain • fast heartbeat • dizziness • fainting • lack of energy • pale skin • black and tarry stools

Mycophenolate Mofetile (MMF)	
Common	**Rare, but may be serious**
	• red blood in stools • bloody vomit • vomit that looks like coffee grounds • yellowing of the skin or eyes

Cyclophosphamide		
Common	**Less Common**	**Rare, but may be serious**
• 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 • death from infection, bleeding, heart failure, allergic reaction, or other causes

Seizures are a potential risk associated with immunosuppressive drugs; however the anti-seizure drug **levetiracetam (Keppra)** is effective at preventing them. Keppra will be given beginning before the 1st dose of sirolimus and continuing through the last dose. Risks of Keppra include hallucinations; fever, chills, body aches, flu symptoms; weakness, lack of coordination; increasing or worsening seizures; and nausea, stomach pain, loss of appetite, itching, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes). Less serious side effects include dizziness, spinning sensation; drowsiness; feeling irritable; headache; runny nose, sore throat; or neck pain. Many anti-seizure drugs, including Keppra, have been shown to increase the risk of depression and suicidal thoughts. Report any new or worsening symptoms of depressed mood to your

doctor. This might include mood or behavior changes, depression, anxiety, or if you are more agitated, hostile, irritable, hyperactive (mentally or physically), or are having thoughts about suicide or hurting yourself.

Risks Associated with the G-CSF (helps with blood count recovery)

G-CSF		
Common	**Less Common**	**Rare, but may be serious**
• With the 1st dose - low blood pressure, fast heart rate, flushing, lightheadedness or feeling faint (not as likely with later doses • Diarrhea • Local skin reaction if injected • Weakness and fatigue	• Mild flu-like syndrome (fever, headache, generalized aches and pains, weakness and fatigue) • Swelling in the hands and feet	• blood clots rarely can lead to pulmonary embolus or stroke • "capillary leak syndrome" or "vascular leak syndrome" in which fluids within the vascular system (veins and capillaries) leaks into the tissue outside the bloodstream – signs include low blood pressure, swelling or rapid weight gain, low urine output, shortness of breath, difficulty breathing, irregular heartbeats, and chest pain

Risks Associated with Bone Marrow Harvest:

Common side effects of marrow collection include:

- back or hip pain
- fatigue
- muscle pain
- headache
- bruising at the collection site
- infection at the collection site

You will feel some soreness in his/her back for a few days, or possibly a week or more.

Risks of Anesthesia

The risk of side effects of anesthesia during bone marrow harvest is similar to that during other surgical procedures. Serious side effects of anesthesia are rare. Common side effects of general anesthesia include sore throat (caused by the breathing tube), mild nausea, and vomiting.

Very rarely patients experience a serious complication due to anesthesia or damage to bone, nerve, or muscle in their hip region.

Risks Associated with Peripheral Stem Cell Harvest

The collection will take place prior your initial therapy. You may begin G-CSF (filgrastim) as a once a day injection under the skin. On the 5th day of G-CSF, the stem cell collection will be started and repeated an additional time (once a day) until a sufficient number of stem cells are collected. Cell collection is done through a process called apheresis. To collect the cells we will use your pheresis capable central line (or a temporary pheresis catheter or two peripheral IVs will be placed if needed). The blood will leave through lumen of the catheter (or through on peripheral IV); pass through a machine that separates out the stem cells, with the rest of the blood returned to you through the other lumen of the cathether (or the other peripheral IV). This process can take up to six hours, during which you will need to sit quietly. Sometiems a second day of pheresis is required to collect enough cells. The apheresis will be done at the University of Minnesota Medical Center, Fairview Blood Donor Center or the Masonic Children's Hospital Journey Clinic Infusion Center. G-CSF will continue until the cell collection is completed.

Possible Risks of Filgrastim (G-CSF)

Possible Risks of Filgrastim (G-CSF)		
common	**less common**	**rare**
none	• bone and muscle pain • abnormal blood tests which suggest that the drug is affecting the liver	• injection site reaction (redness, pain, or swelling) • allergic reaction • spleen enlargement or rupture • trouble breathing or coughing up blood

Risks of Apheresis (Collection of the Stem Cells):

There are risks to the apheresis process including

- bruising and/or bleeding where the peripheral IVs are inserted or pheresis catheter placed for the apheresis,
- reaction to citrate, the drug used as to prevent your blood from clotting during the collection- Citrate sometimes causes temporary numbness of the fingertips or around the mouth. Should you experience any numbness, you must tell the nurse operating the machine, since if not corrected this complication could progress to severe muscle cramps
- loss of platelets with the of stem cells collection - If your level of platelets falls too low, you may bruise or bleed more easily. If you receive a cut it may take several minutes for the bleeding to stop. It may take 7 to 10 days for your platelet level to return to normal.
- loss of blood (up to ½ pint) if the tubing breaks – this is very rare

Appendix 3
For cALD Patients Only

Anti-Oxidant And Anti-Inflammatory (AO/AI) Supportive Care

N-acetylcysteine can cause nausea, vomiting, and diarrhea or constipation. Rarely, it can cause rashes, fever, headache, drowsiness, low blood pressure, and liver problems.

When inhaled, it can also cause swelling in the mouth, runny nose, drowsiness, clamminess, and chest tightness.

N-acetyl cysteine has an unpleasant odor that may make it hard to take.

Celecoxib:		
Common	**Less Common**	**Rare**
• cough • fever • rash • sneezing • sore throat	• vomiting • heartburn • nausea • diarrhea • stomach pain • wheezing • headache • tiredness (fatigue), weakness • increased sensitivity of skin to sunlight (higher risk of sunburn) • loss of appetite • liver function test changes • bloating or swelling, especially of the legs and feet* • peptic (stomach) ulcers • bleeding from the stomach or intestines • abnormal blood tests which suggest that the drug is affecting the liver	• decreased hearing • vision changes • double vision • hepatitis (liver inflammation) • liver damage, which may cause yellow skin or eyes (jaundice) • rash and itching • high blood pressure • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) and tiredness • urinary tract infection • kidney damage (usually gets better after medicine is stopped) • kidney failure • blood in urine • stroke (higher risk with long term use) • heart attack (higher risk with long term use) • anxiety • severe allergic reaction with trouble breathing, raised itchy

Celecoxib:		
Common	**Less Common**	**Rare**
		welts on the skin, or swelling of the face, mouth, or throat • heart attack or stroke

Vitamin E may cause allergic skin reactions (inflammation or itching), blurred vision, changes in cholesterol levels, changes in insulin resistance, diarrhea, dizziness, fatigue, flu-like symptoms, headache, heart conditions, increased risk of death, increased risk of fainting or falls, increased risk of heart failure, increased risk of high blood pressure in pregnancy, increased risk of stroke, increased risk of tuberculosis, kidney dysfunction, nausea, severe response to infection (in preterm babies), sexual dysfunction, stomach pain, vision loss, and weakness.

Alpha Lipoic Acid is generally safe, but may cause a rash or lower blood sugar. People at risk for thiamine deficiency should take a thiamine supplement.

Appendix 4
For Hemoglobinopathy Patients Only

Hydroxyurea		
Common	**Less Common**	**Rare**
• Cough or hoarseness • fever or chills • lower back or side pain • painful or difficult urination	• Black, tarry stools • blackening of the fingernails and toenails • blood in the urine or stools • pinpoint red spots on the skin • sores in the mouth and on the lips • unusual bleeding or bruising	• Confusion • convulsions (seizures) • difficulty with urination • dizziness • headache • joint pain • seeing, hearing, or feeling things that are not there • swelling of the feet or lower legs

Appendix 5 – For Female Subjects Only

Ovarian Transposition is a surgery that moves the ovaries out of the field of radiation. Some subjects may elect to have this procedure in order to improve their chances of having children after cancer treatment. The surgical team will explain more about this procedure.

If you decide to have ovarian transposition, then your treatment schedule would be rearranged and your total body irradiation occur on day -10, rather than day -1. On day -8, the ovaries will be moved back to their original position. Day -1 would become a rest day:

Day	Drug or Procedure	
Conditioning Regimen		
-10	Radiation	One time
-9, -8, -7, -6*	ATG	Infused in your IV over 6 hours
-7	Thiotepa	Infused two times in your IV over 2 hours
-6, -5	Cytoxan	Infused in your IV over 2 hours
-6, -5, -4, -3, -2	Fludarabine	Infused in your IV over 1 hour
-1	Rest	
Transplant		
0	Donor bone marrow cell (transplant)	Infused over less than 1 hour in your catheter
Post Transplant Drugs		
+3, +4	cyclophosphamide	1 daily dose in your catheter
+5	Begin sirolimus	2 or 3 (depending on your body weight) daily doses in your catheter
+5	Begin MMF	3 daily dose in your catheter or as a pill if you are able to swallow pills
Supportive Care		
+5	Begin G-CSF to help blood counts recover	Infused in your IV