The Children's Hospital *of* Philadelphia®

Informed Consent Form and HIPAA Authorization

Study Title: 13BT051 - UNRELATED AND PARTIALLY MATCHED RELATED DONOR PERIPHERAL STEM CELL TRANSPLANTATION WITH alpha/beta T CELL AND B CELL DEPLETION FOR PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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You, or your child, may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff. If you are a parent or legal guardian who is giving permission for a child or an adult that is unable to consent for him/her self, please note that the word "you" refers to either the child or the adult not able to self consent.

Why are you being asked to take part in this study?

You are being asked to take part in this research study because you have leukemia or a blood disorder for which a blood "stem" cell transplant may improve the chance of cure. There is a higher rate of complications using cells from an unrelated or partially matched related donor. T cells within the donor cells may cause a complication called graft vs. host disease (GVHD). GVHD is described in this consent form. We want to use the CliniMACs device to remove alpha/beta T cells. This is called T depletion.

In addition, the CliniMACs device will be used to remove B cells. B cells sometimes can contribute to patients developing a virus that leads to enlarged lymph nodes. This is known as Epstein Bar Virus (EBV) associated lymphoproliferative disorder.

What is the purpose of this research study?

The purpose of this research study is to test a new method of cell processing for stem cell transplants with an unrelated donor or partially matched related donor. The new method is called alpha/beta T cell and B cell depletion. We want to see if this method can reduce some of the complications of the transplant and decrease the time it takes for the new stem cells to grow in the body.

CliniMACs is an investigational device, which means that the United States Food and Drug Administration (FDA) has not approved it for marketing.

The use of the CliniMACs device for alpha/beta T and B cell depletion is experimental and is considered research. This means that it has not been approved by the Food and Drug Administration (FDA) for commercial use. However, the FDA has agreed to the use this investigational cell processing device in this study.

Donor cells (either from an unrelated donor who is at least a partial match or a related partially matched donor) will be processed with the CliniMACs device. If your stem cells were collected from an unrelated donor, the final product infused following the alpha/beta/CD19+ depletion is considered an investigational product.

In order for you to participate in this study, you must have a suitable donor who is able and willing to undergo apheresis, or collection of blood stem cells. Your donor will sign a separate consent form to donate stem cells. Not all potential donors are able and willing to do this procedure.

How many people will take part?

About 140 people will take part in the study, including approximately 110 participants from CHOP.

What is involved in the study?

If you agree to participate in this study, you will have a blood stem cell transplant. We will take blood stem cells from an unrelated or partially matched related donor and process them with the CliniMACs device, as described above.

The majority of the procedures that will be done during this study are considered "**standard of care."** This means that you would have these procedures done if you were having a transplant outside of this study (without stem cell processing with the CliniMACs device). However, if you do not have a tissue type match, we might be unable to perform a transplant.

The details of the transplant process and follow-up after transplant are given below:

Central Venous Cather (Standard of Care): You will have a central venous catheter (CVL, Broviac) inserted upon admission. You will receive a separate consent form for this. You will be admitted to a transplant room in the Blood and Marrow Transplant (BMT) Unit during the conditioning. Placement of the CVL is considered standard of care for transplant.

Conditioning (Standard of Care):

You will receive "conditioning," or high-dose chemotherapy and sometimes, radiation before the infusion of the donor blood cells.

The purpose of the conditioning is to:

- Get rid of the leukemia, if previously diagnosed

- "Make space" in the bone marrow for new bone marrow to grow
- Suppress your immune system to help your body accept the stem cells from your donor.

  The conditioning regimen you receive will be explained in detail. A document called a roadmap will be provided to you as well. The conditioning agents used for this protocol are:

- **Thiotepa -** This is a chemotherapy drug that will be given to you in a vein over 2 hours, for 2 days
- **Cyclophophamide -** This is a chemotherapy drug that will be given in a vein over 2 hours, for 2 days. You will start this after you complete the Thiotepa.
- **Total Body Irradiation** – This will be done twice a day for 3 days, before or after the chemotherapy. The lungs will be shielded for the last two treatments.

  *If you are less than 2 years of age, have received radiation in the past, or are at increased risk of organ toxicities with total body irradiation, a drug called **Busulfan**, may be given in a vein, 4 times a day for 4 days, instead of radiation, before the rest of the chemotherapy. We would do this to avoid specific side effects of radiation.

- **Thymoglobulin -**This will be given to you in a vein for 3 days. If you are receiving stem cells from an unrelated donor, you will not be given any Thymoglobulin.
- **Rituximab -** will be given if you are found to have a positive blood test that indicates you had a past infection of the Epstein Barr Virus. You will receive one dose of Rituximab the day after your transplant.

Use of an Investigational Device called CliniMACs (Research): The CliniMACs device is used to remove alpha/beta T cells that may cause graft vs. host disease (GVHD) and B cells that carry Epstein-Barr virus. For a patient that does not have a tissue type matched related or unrelated donor, the risk of GVHD is extremely high. Elimination of the alpha/beta T cells may decrease the risk of GVHD. You must have either an unrelated donor who is at least a partial match, or a partially matched related donor available for this study. The donor will undergo a process called apheresis to collect their blood making stem cells. The blood stem cells will be processed in the Stem Cell Laboratory at the Children's Hospital of Philadelphia with the CliniMACs device following conditioning. We will attempt to provide high doses of stem cells to help with engraftment of the new bone marrow.

Stem Cell Infusion (Research): After your conditioning is completed, you will receive a stem cell transplant. The processed donor stem cells will be given to you in a vein. This process takes about one hour. The CliniMACs device will be used to remove alpha/beta T cells and B cells from the donor cells before we give them to you.

The time it takes for the donor blood cells to grow varies, but there should be evidence of engraftment (growth of new cells in the bone marrow) by Day 30. During the time it

takes for blood counts to normalize, you will require transfusions of blood cells and platelets, and antibiotics to help fight infection.

We will review your medical chart throughout the study to collect information about you and your health.

Discharge and immediate follow up (Standard of Care): You will be able to leave the hospital when your clinical team determines it is safe. However, it is important that we continue to closely monitor you for problems relating to the transplant. We will continue to see you weekly, for the first 2-3 months after the transplant. This is considered standard of care for anyone who has had a stem cell transplant. At your weekly visits, we will monitor your blood counts, chemistries and immune function. We will check to see what percentage of your donor's stem cells is in your blood. We will see you yearly, to monitor for late effects following bone marrow transplant and you will be given a schedule of tests at that time. You will receive intravenous gammaglobulin (IVIG) to help decrease the possibility of a serious viral infection. IVIG is given every 2 weeks for 3 months. We will then follow your gammaglobulin levels to determine when and if you need additional infusions.

Other laboratory tests (Standard of Care): We will check your blood every 2-4 weeks with a test that determines the % of donor cells/patient cells (chimerism). It is not necessary for patients with non-malignant disease to have 100% donor cells for cure of their underlying disease, but they should have stable chimerism over the first year. Blood tests also will be performed periodically throughout the first two years to evaluate the growth of the new immune system.

How long will you be in this study?

You will be able to leave the hospital when there are enough white blood cells to help fight infection, there is no active infection, and there is control of GVHD (if it occurs). However, it is important that we continue to closely monitor you for problems relating to the transplant. We will continue to see you weekly for the first 2-3 months after the transplant. This is considered standard of care for anyone who has had a stem cell transplant. At your weekly visits, you will have blood tests so we can monitor your blood counts, chemistries and immune function. We will check to see what percentage of your donor's stem cells is in your blood. After that, you will be seen monthly for 12 months, at 1 ½ years, 2 years, and then yearly up to 5 years to monitor for late effects following transplant. You will be given a schedule of tests at that time. **This is all considered standard of care following a transplant.**

What are the study procedures?
If you agree to participate in this study, the following will occur:

Review of medical records for research purposes

Use of a Device called CliniMACs (Investigational)

You must have either an unrelated donor who is a close match, or a partially matched related donor available for this investigational treatment. The donor must agree to undergo a process called apheresis to collect their blood making stem cells.

The blood stem cells will be processed in the Stem Cell Laboratory at the Children's Hospital of Philadelphia with the CliniMACs device before infusion.

What are the risks of this study?

Taking part in a research study involves inconveniences and risks. If you have any questions about any of the possible risks listed below, you should talk to your study doctor or your regular doctor.

While in this study, you are at risk for the following side effects:

Risks of T and B cell Depletion using the CliniMACs device:

Graft rejection, which occurs when the transplant recipient's body does not accept the transfused donor stem cells, is more common in T-depleted transplants than in transplants where the T cells are not removed. It is also possible the new immune system may grow very slowly, which can increase the risk of infection. There is a risk of infection contamination from the processing procedure, but every precaution is taken to prevent this as the cells are processed under a sterile hood. Stem cell transplants that have had T cells removed have been associated with a particular type of infection caused by Epstein-Barr virus. This may cause life-threatening problems, and there is not always a satisfactory treatment. However, CliniMACs processing will also remove B cells to help prevent this type of infection.

Reproductive Risks

For female subjects:

If you are pregnant or nursing, you will not be allowed to participate in this study. If you are sexually active you are to not have intercourse during the conditioning period and the initial hospitalization for your transplant. If you have questions about sexual activity, talk to your doctor or the researcher and they will provide you with information on when it is safe to resume sexual activity and use of contraception. You should contact Dr. Nancy Bunin at once if you become pregnant during this research study.

For male subjects:

If you are sexually active you are to not have intercourse during the conditioning period and the initial hospitalization for your transplant. If you have questions about sexual activity, talk to your doctor or the researcher and they will provide you with information on when it is safe to resume sexual activity and use of contraception. You should contact Dr. Nancy Bunin at once if you become pregnant during this research study.

Are there any benefits to taking part in this study?

Potential Benefits using the CliniMACs device for T and B cell Depletion:

Use of high doses of peripheral blood cells has been associated with faster engraftment (growth of new cells in the bone marrow), decreased transfusion needs, and decreased infections. Removing the T cells may decrease the risk of GVHD. Removing the B cells reduces the risk of Epstein - Barr virus. The overall benefit of a stem cell transplant is possible cure of the underlying disease.

We hope that the research therapy will improve or cure your disease, however, we cannot guarantee or promise that you will directly benefit by participating in this study.

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record. Please consider the study time commitments and responsibilities as a research subject when making your decision about participating in this study

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP.

If you decide not to take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason. However, please be aware that it would be life-threatening to not have a transplant after starting conditioning. You would get a transplant after conditioning as part of your usual care, regardless of whether you participate in this study or not. After starting conditioning, you can withdraw from the research and not have the cells to be transplanted processed using the CliniMACs device.

If you decide to stop participating in the study, it is important that you discuss this with the study doctor first, so she can make sure that you stop safely.

Can the study doctor take you out of the study early?

The study doctor may take you off of the study if:

The investigator can remove you from study if it is decided that this would be in your best interest.

What choices do you have other than this study?

There are options for you other than this study including:

Alternatives to this treatment may include using myeloablative conditioning with cord blood, instead of peripheral stem cells, other experimental therapy or supportive care only.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

As part of this research, health information about you will be collected. This will include information from medical records regarding your transplant. This is inclusive of information regarding you illness and general condition prior to, during and after your transplant. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The results of this study may be shown at meetings and published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized staff at CHOP and Children's Hospital of Wisconsin;
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the Department of Health and Human Services, Office for Human Research Protections.
- The Food and Drug Administration (FDA) and other government agencies involved in the oversight of this research;
- Groups who monitor the safety of the study (e.g. the Penn Cancer Center);
- Laboratories who will test your blood samples for the study;
- The International Bone Marrow Transplant Registry. The Children's Hospital of Philadelphia Blood and Marrow Transplant Program is an accredited transplant center. In order to maintain this accreditation, we must provide limited information regarding your transplant to this group. Information will be provided in a way that does not identify you;
- The National Marrow Donor Program, if you receive your stem cell product from an unrelated donor;
- People from agencies and organizations that perform independent accreditation and/or oversight of research, such as the Department of Health and Human Services, Office for Human Research Protections; and
- Public health authorities that are required by law to receive information for the prevention or control of disease, injury, disability or child abuse.

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

There is no set time for destroying the information that will be collected for this study.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, it is preferred that you inform the investigator in writing.

Dr. Nancy Bunin
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104

In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

Financial Information

Will there be any additional costs?

While you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance. This includes the costs of the experimental processing using the CliniMACs device. Your insurance company must agree to reimbursement for the treatment before hospital admission.

Will you be paid for taking part in this study?

You will not receive any payments for taking part in this study.

Who is funding this research study?

The Division of Oncology/Blood and Marrow Transplant Program at The Children's Hospital of Philadelphia is funding this research. Please ask Dr. Bunin if you have any questions about how this study is funded.

What if you have questions about the study?

If you have questions about the study, call the study doctor, Dr. Nancy Bunin at (215) 590-2255. You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-590-2830.

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, the Web site will include a summary of the results. You can search this Web site at any time.

What happens if you are injured during the study?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency medical care. The Hospital does not offer financial compensation or payment for injuries due to participation in this research. You and your insurance company will be billed for the costs of any care or injuries.

If you think you have been injured from taking part in this study, call Dr. Nancy Bunin at (215) 590-2255. She can go over things with you, let you know of resources that may be available and give you information on what you need to do.

In case of injury resulting from this study, you will not lose any legal rights by signing this form.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research

The research study and consent form have been explained to you by:

Person Obtaining Consent	Signature of Person Obtaining Consent
	Date

By signing this form, you are indicating that you have had your questions answered, you agree to take part in this research study and if you are giving permission for a child or consent for an adult to participate in this research study, you are legally authorized to consent to the child's or adult's participation. You are also agreeing to let CHOP use and share the health information that will be collected for this study, as explained above. If you don't agree to the collection, use and sharing of health information, you cannot participate in this study.
NOTE: *A foster parent is not legally authorized to consent for a foster child's participation.*

Name of Subject	
Signature of Subject (18 years or older)	Date
Name of Authorized Representative (if different than subject)	Relation to subject: ☐ Parent ☐ Legal Guardian ☐ Legally Authorized Representative
Signature of Authorized Representative	Date

STUDY SUMMARY SIGNATURE PAGES FOR NON-ENGLISH SPEAKING SUBJECTS

Consent to Take Part in this Research Study and
Authorization to Disclose Health Information

Name of Subject

Name of Authorized Representative
(if different than subject)

Relation to subject:
☐ Parent ☐ Legal Guardian

The research study and consent form have been explained to the subject or parent/legal guardian.

By signing this form, you are indicating that you have answered the subject's or parent's/legal guardian's questions, they have agreed to take part in this research study and they are legally authorized to consent to their or their child's participation. They have also agreed to let CHOP use and share their or their child's health information as explained above. If they don't agree to the collection, use and sharing of their or their child's health information, they cannot participate in this study.

Person Obtaining Consent

Signature of Person Obtaining Consent

Date:

Witness/Interpreter

By signing this form, you are indicating that

- The information in the Summary Document as well as any additional information conveyed by the person obtaining consent was presented to the subject in a language preferred by and understandable to the subject; and
- The subject's questions were interpreted and the responses of the person obtaining consent were presented in a language preferred by and understandable to the subject.
- At the conclusion of the consent conference, the subject was asked in a language preferred by and understandable to the subject if s/he understood the information in the Summary Document as well as any additional information conveyed by the person obtaining consent (including responses to the subject's questions) and responded affirmatively.

Name of Witness/Interpreter

Signature of Witness/Interpreter

Date:

Appendix I

Standard of Care Risks

Risks of drugs and/or radiation used in the conditioning and for GVHD prevention include:

ANTI-THYMOCYTE GLOBULIN (ALG, Thymoglobulin):

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving ATG, more than 20 and up to 100 may have:
• Fever, hives • Decrease in number of lymphocytes in blood, increased risk of infections

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving ATG, from 4 to 20 may have:
• Wheezing, trouble breathing, low blood pressure

RARE SIDE EFFECTS, AND SERIOUS In 100 people receiving ATG , 3 or fewer may have:
• Increase in viral infections, lymphoma from Epstein Barr virus

BUSULFAN (Myleran):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Busulfan, more than 20 and up to 100 may have:
• Anemia which may require blood transfusions • Infection, especially when white blood cell count is low • Bruising, bleeding • Diarrhea, nausea, vomiting, loss of appetite • Sores in mouth which may cause difficulty swallowing • Belly pain • Headache • Difficulty sleeping • Worry • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Busulfan, from 4 to 20 may have:
• Seizure • Internal bleeding which may cause coughing up blood • Damage to or scarring of the lungs • Damage to the liver • Menopause

RARE, AND SERIOUS In 100 people receiving Busulfan, 3 or fewer may have:
• Fluid around heart • Cancer of bone marrow caused by chemotherapy

CYCLOPHOSPHAMIDE (CTX, Cytoxan):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require transfusion • Bruising, bleeding • Blood in urine • Nausea, vomiting, diarrhea, loss of appetite, pain in belly • Sores in mouth which may cause difficulty swallowing • Absence of menstrual period which may decrease the ability to have children • Hair loss, skin changes, rash, change in nails

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, from 4 to 20 may have:
• Fluid around the heart • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Loss or absence of sperm which may lead to an inability to father children

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • Swelling of the body including the brain which may cause dizziness, confusion • Damage to the lungs or scarring of the lungs which may cause shortness of breath • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Sinusodial obstructive syndrome (SOS) which may cause damage to the liver, yellowing of eyes and skin, swelling • Kidney damage which may cause swelling, may require dialysis • A new cancer (including leukemia) resulting from treatment of a prior cancer • Stevens-Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body

CYCLOSPORIN A:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving cyclosporine, more than 20 and up to 100 may have:
• High blood pressure • Kidney problems • Headaches • Nausea • Vomiting • Stomach pain or indigestion • Swelling of the hands or feet

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving cyclosporine, from 4 to 20 may have:
• Tremors • Increased hair growth

RARE SIDE EFFECTS, AND SERIOUS In 100 people receiving cyclosporine, 3 or fewer may have:
• Muscle cramps • Numbness and tingling of the hands or feet • Seizure

TACROLIMUS:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Tacrolimus, more than 20 and up to 100 may have:
• High blood pressure which may cause dizziness, blurred vision • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Kidney damage which may cause swelling, may require dialysis • Constipation, diarrhea, nausea, vomiting • Diabetes • Abnormal body movement • Feeling of "pins and needles" in arms and legs • Headache • Dizziness • Difficulty sleeping • Swelling of the body • Fever • Hair loss • Itching, rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Tacrolimus, from 4 to 20 may have:
• Damage to organs (heart, lungs, brain, others) which may cause changes in thinking, confusion, memory loss or shortness of breath • Heart attack or failure which may cause chest pain, swelling of ankles, and tiredness • Change in the heart rhythm, abnormal heartbeat, or heart stops beating • Brain damage, which may cause headache, seizure, blindness • A tear or a hole in the bowels which may cause belly pain or that may require surgery • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS In 100 people receiving Tacrolimus, 3 or fewer may have:
• A new cancer resulting from treatment of a prior cancer

THIOTEPA (Tespa, Tspa):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Thiotepa, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may cause tireness, or may require transfusion • Bruising, bleeding • Sores in mouth which may cause difficulty swallowing • Prior viral infection that returns which may cause diarrhea, blindness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Thiotepa, from 4 to 20 may have:
• Bleeding from multiple sites including the brain and depending on the site may cause headache, confusion, belly pain, black tarry stool, or blood in vomit • Damage to the liver which may cause yellowing of eyes and skin, swelling • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Seizure • Blood in urine

RARE, AND SERIOUS In 100 people receiving Thiotepa, 3 or fewer may have:
• None

RITUXIMAB (Rituxan):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may require blood transfusion • Nausea • Reaction during or following infusion of the drug • Chills, fever • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab, from 4 to 20 may have:
• Heart attack which may cause chest pain, shortness of breath • Abnormal heartbeat which may cause fainting • Low blood pressure which may cause feeling faint • Swelling of arms, legs • Damage to the lungs which may result in shortness of breath • Blockage of the airway which may cause shortness of breath, cough, wheezing • Swelling and redness of the throat and sinuses (might not be caused by infection) which may cause difficulty breathing and swallowing • Bruising, bleeding • Prior liver infection that returns which may cause yellow eyes and skin, tiredness • Kidney damage which may require dialysis • A tear or a hole in the bowels that may require surgery • Diarrhea • Headache • Cold symptoms such as stuffy nose, sneezing, sore throat • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

RARE, AND SERIOUS In 100 people receiving Rituximab, 3 or fewer may have:
• Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability • Heart stops beating

TOTAL BODY IRRADIATION:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving TBI, more than 20 and up to 100 may have:
• Slight redness of the skin • Nausea • Poor appetite • Sleepiness • Headache • Poor growth • Sterility •

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving TBI, from 4 to 20 may have:
• Inflammation of salivary glands • Lung scarring • Cataracts • Decrease thyroid function

RARE SIDE EFFECTS, AND SERIOUS In 100 people receiving TBI, 3 or fewer may have:
• Inflammation of the lungs with trouble breathing • New cancer

Appendix II

Standard of Care Risks

Risks of Hematopoietic Progenitor Cell (HPC) Transplant

- **Infections:** One of the goals of the chemotherapy and/or radiation that you will receive as part of your transplant is to weaken your immune system so that your body will accept the cells of your donor. Your immune system is made up of white blood cells that fight infections. Chemotherapy and radiation weakens your immune system by making white blood cells go away. After transplant, your donor's bone marrow cells will make new white blood cells. However, it takes time for these new white blood cells to be made, and your immune system will not return to normal for many months after transplant. Before these white blood cells fully recover, you will be at high risk for infections. These infections can be severe. The highest risk for infection occurs in the first few weeks after transplant. You

will receive medicines including antibiotics to prevent infections. Even with these medicines, serious infections may still happen. Infections are caused by different types of small organisms or germs. Bacterial infections are the most common type after transplant. Viral infections can also happen after transplant. These infections can be caused by a new virus that is caught from a sick person. Virus infections can also be caused by some types of viruses that your body was exposed to much earlier in your life and never left your body. These types of viruses can start to grow again and cause infections when your immune system is weakened after transplant. This is called viral reactivation. Other infections after transplant include infections with fungi and parasites. These are rare. Most of the time, we can successfully treat each of these types of infections with antibiotics or other immune system therapies without any lasting damage to your body. These treatments can take several weeks and lead to longer time spent in the hospital. However, in some cases, these infections can cause lasting damage to organs or even death.

- **Bleeding:** Platelets are another type of blood cell that are decreased by chemotherapy and radiation. Platelets help prevent bleeding by helping blood to clot. After transplant, patients have very low levels of platelets for several weeks. While platelets are low, there is a risk of bleeding. Mild bleeding is common and may include nosebleeds, bruises, or small amounts of blood seen in mucous coming from your mouth. More severe bleeding can occur in the stomach/intestines, the lungs, and the brain after transplant. Usually, we are successful at preventing major bleeding after transplant by transfusing platelets. However, platelet transfusions do not always prevent bleeding. Some patients may also develop painful bleeding in the bladder/urine that can last several weeks.

- **Graft vs. host disease (GVHD):** While immune cells from your donor help prevent infections and are needed to make your transplant a success, immune cells from your donor might attack organs and tissues in your body causing GVHD. The two types of GVHD are called acute GVHD and chronic GVHD.

    - **Acute GVHD:** Acute GVHD usually happens in the first 3 months after transplant, though rarely it can begin later. Acute GVHD can cause damage to three parts of your body: your skin, your liver, or your intestines. Acute skin GVHD can cause red skin or an itchy rash. Rarely, severe skin GVHD can cause blisters like burns. Intestinal GVHD can cause belly pain and diarrhea. The diarrhea can be bloody. Liver GVHD can cause jaundice and weight gain due to build-up of fluid in the body. Very severe acute GVHD can cause death.

    - **Chronic GVHD:** Chronic GVHD is more likely to develop in people who had acute GVHD. It can also happen in people who did not have acute GVHD. Chronic GVHD occurs later than 3 months after transplant. Chronic GVHD can cause problems with many parts of the body. It can damage skin, liver, stomach, intestine, joints, lungs, muscles, eyes, the lining of the mouth, or other organs. Scarring and other permanent damage may happen. Severe chronic GVHD can cause death.

- **GVHD treatment:** Medications may be used to prevent GVHD. Special types of processing may be performed on the donor cells before you receive them to prevent GVHD. Your doctors will explain if medicines, special processing, or both will be used. Even with medicines and special processing, GVHD may still happen. GVHD is treated with medicines that often suppress the immune system and increase the risk of severe infections. Mild skin GVHD can often be treated with creams alone. While patients may respond quickly, in some cases it may take a long time for GVHD to get better.

- **Organ damage:** Your body is made up of many organs. Transplant may cause damage to these organs. Organ damage can happen from chemotherapy, radiation, GVHD, or other side effects like infections. Some organs including your lungs, kidneys and liver are more likely to get hurt after transplant than other organs like your heart or brain. While most of the time organ damage caused by transplant is reversible, sometimes organ damage is permanent.

    - **Mucositis and diarrhea:** Chemotherapy and radiation may hurt the inside of your mouth, causing painful sores. Chemotherapy and radiation may also hurt the lining of your stomach and intestines, causing nausea, pain, or diarrhea. This damage is called mucositis. Pain medicine is usually needed when mucositis is severe. Often, patients are not able to eat when mucositis is severe and require nutrition that is given through a feeding tube or through IV fluids. Mucositis gets better after transplant.

    - **Liver damage including sinusoidal obstruction syndrome (SOS):** Many medications that are part of transplant can damage the liver. Liver damage is usually temporary, but rarely it can be permanent. SOS is a certain type of liver damage that is also called Veno-Occlusive Disease (VOD). This is a side effect caused by certain chemotherapy medicines or radiation used in transplant. SOS can cause yellow eyes and skin called jaundice. SOS can make fluid build-up in the body causing weight gain and feet/leg swelling. It can cause fluid build-up and swelling in the belly, which is called ascites. Ascites can be painful and make it hard to breathe. We have medicines to treat SOS. Most of the time these medicines work, but it may take several weeks of treatment in the hospital before symptoms improve. Rarely, SOS can be fatal.

    - **Kidney damage including thrombotic microangiopathy (TMA):** Chemotherapy and other medicines given in transplant may cause damage to the kidneys. Kidneys are the organs in your body that makes urine. Infections and medication side effects that occur during transplant can also damage your kidneys. One type of kidney damage is called TMA. TMA can usually be treated with special medicines. Severe TMA can hurt other organs and rarely, it can cause death.

    - **Lung damage including capillary leak syndrome and idiopathic pneumonia syndrome (IPS):** Your lungs are the organs that help you breathe. Lungs can be

damaged from medicines used in transplant. Lungs can also be damaged from side effects of transplant including infections and GVHD. Lungs can also be damaged when new bloods cells first start to be made after transplant. This is called engraftment syndrome. Another type of lung damage after transplant is called capillary leak syndrome. With capillary leak syndrome your blood vessels become leaky. Fluid builds up in and around the lungs, causing trouble breathing. Most of the time, capillary leak syndrome can be treated. Rarely, patients can develop a type of lung damage after transplant called IPS. We do not know why some patients develop IPS. IPS may cause permanent lung damage, and severe IPS may cause death. All types of lung damage can be serious. Some people with lung damage need to go onto machines to help them breathe. These machines are called ventilators.

- **Unexpected organ damage and multi-organ failure:** Rarely transplant can damage other organs. These include your heart and brain. Sometimes many organs may become damaged at the same time. This is called multi-organ failure. Multi-organ failure often requires you to be treated in the intensive care unit (ICU). Multi-organ failure has a high risk of death.

- **Late effects:** All of the side effects mentioned so far happen soon after transplant. There can also be long-term side effects of transplant. Some of these long-term side effects may not happen until years after transplant. These can be long-term side effects to organs including the heart, kidney, lungs, and brain. Damage to glands that make hormones can also occur. This damage can decrease your growth and cause you to be shorter than you would have been if you did not have a transplant. These hormone effects can cause problems with going through puberty. For females, these side effects can cause early menopause. These effects can also make it so you cannot have children naturally. Some hormone problems can be treated with medicines. Another long-term side effect of transplant is a higher risk of cancer due to the chemotherapy or radiation you will receive. Sometimes we can do screening for these cancers, and if caught early, these "secondary" cancers may be easier to treat. Sometimes they are very hard to treat and can be life threatening.

- **Relapse or disease recurrence:** Even if transplant initially cures your disease, it may stop working. The disease you received a transplant to fix may come back. This is called relapse if the transplant is for cancer. It is called disease recurrence if the transplant is not for cancer. Relapse or disease recurrence usually happens within the first two years after transplantation. Sometimes a second transplant can be performed.

- **Graft failure:** Graft failure is when the transplanted cells don't work well enough to continue making blood cells over time. Graft failure has two types. Type one is called primary graft failure. Primary graft failure means the newly transplanted cells never make enough blood cells after transplant. The other type is called secondary graft failure. Secondary graft failure means the transplant worked at first, but then it fails. Graft failure can happen from many reasons. Sometimes your immune system attacks the donor cells. This immune attack is called rejection. Sometimes graft failure occurs due to problems

that occur in the donor cells due to infection or other stresses. Finally, graft failure may occur because of regrowth of your own blood cells that crowd out and remove the donor cells. This is called autologous reconstitution. If graft failure occurs without regrowth of your own blood cells, it can cause aplasia. Aplasia means your bone marrow is empty and makes no blood cells. Aplasia requires an emergency second transplant.