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Name of Subject

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TITLE OF RESEARCH PROJECT: CHP 894 REDUCED INTENSITY CONDITIONING (RIC) FOR NON-MALIGNANT DISORDERS – AMENDMENT # 8

IRB #: 2008-1-5658

August 30, 2017

**CONSENT TO PARTICIPATE IN A RESEARCH STUDY AND AUTHORIZATION
TO DISCLOSE HEALTH INFORMATION**

INVITATION TO PARTICIPATE

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. Parents or legal guardians, who are giving permission for a child, please note: in the sections that follow the word 'you' refers to 'your child.'

This study is for subjects who receive blood or marrow cells from a matched relative or an unrelated donor. For subject less than 12 months of age without a matched related or unrelated donor we will use a partially matched related donor.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

A blood or marrow transplant has been recommended by your doctor because your child has a disease that can be cured only by transplanting blood or bone marrow cells from another person to replace his/her bone marrow.

WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

The purpose of this study is to see if we can engraft (grow) donor cells and cure the underlying disease by using Reduced Intensity Conditioning (RIC) before receiving the donor blood or marrow cells. RIC involves giving medicines that suppress the immune system before giving the donor stem cells. It does not completely eliminate your blood making cells in your bone marrow. This is in contrast to standard myeloablative conditioning that would completely "wipe out" your bone marrow with high doses of chemotherapy and radiation.

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Why use RIC?

There are different reasons, based upon the individual subject, why we would like to study RIC. Many non-malignant (non-cancer) diseases may not require a fully myeloablative conditioning for cure, as long as there are sufficient numbers of donor cells that grow to correct the underlying problem. Myeloablative conditioning is more toxic to organs, such as the liver, lungs, and kidneys, than RIC, and may be more likely to have late effects on growth, development, and gland function.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

We expect about 75 children to be enrolled at CHOP.

WHAT IS INVOLVED IN THIS RESEARCH STUDY?

Your child will have a central venous catheter (CVL, Broviac) inserted upon admission. You will receive a separate consent form for this. Your child will be admitted to a transplant room in the Blood and Marrow Transplant (BMT) Unit during the conditioning. Depending upon your diagnosis you will receive one of three RIC treatments. They differ by the timing of Alemtuzumab (Campath). If you have been diagnosed with Thalassemia, you will receive two additional drugs in your conditioning.

For children with sickle cell disease, IPEX

The treatment plan is:

Day	Treatment
-22	Inpatient: Alemtuzumab (Campath) test dose IV or SQ (subcutaneously) over 2 hours
-21 to -19	Alemtuzumab IV/ SQ
-7 to -3	Readmission to hospital Fludarabine IV
-2	Melphalan IV
-1	Begin cyclosporine infusion
0	Transplant: Bone marrow or cord blood infusion
+1	Begin MMF by mouth
+7	Begin G-CSF SQ

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For children with Thalassemia Major:

	Treatment
-50 to -22	Hydroxyurea orally
-22	Inpatient: Alemtuzumab (Campath) test dose IV or SQ (subcutaneously) over 2 hours
-21 to -19	Alemtuzumab IV/ SQ
-7 to -3	Readmission to hospital Fludarabine IV
-3	Thiotepa
-2	Melphalan IV
-1	Begin cyclosporine infusion
0	Transplant: Bone marrow or cord blood infusion
+1	Begin MMF by mouth
+7	Begin G-CSF SQ

For children > 6 months with immune deficiencies, hemophagocytic disorders (HLH):

Day	Treatment
-14 to -10	Admission Alemtuzumab (Campath) IV or SQ (subcutaneously)
-7 to -3	Fludarabine IV
-2	Melphalan 140 mg/m ² IV
-1	Cyclosporine infusion starts
0	Bone marrow or cord blood infusion
+1	Begin MMF by mouth
+7	Begin G-CSF SQ

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For children < 6 months with immunodeficiencies

Day	Treatment
-8	Alemtuzumab (Campath) IV or SQ (subcutaneously)
-7	Alemtuzumab (Campath) IV or SQ (subcutaneously)
-6	Alemtuzumab (Campath) IV or SQ (subcutaneously) Busulfan IV Fludarabine IV
-5	Alemtuzumab (Campath) IV or SQ (subcutaneously) Busulfan IV Fludarabine IV
-4	Alemtuzumab (Campath) IV or SQ (subcutaneously) Fludarabine IV
-3	Fludarabine IV
-2	Fludarabine IV Begin Cyclosporine infusion
-1	Rest
0	Transplant: Bone marrow or cord blood infusion
+1	Begin MMF by mouth
+7	Begin G-CSF SQ

Your child will receive medications before the Alemtuzumab (Campath), as Campath can cause allergic reactions. These medications include diphenhydramine (Benadryl), acetaminophen (Tylenol) and steroids (methylprednisolone).

Transplant: The donor bone marrow or blood cells will be given on day 0 intravenously.

G-CSF (Neupogen) will be given subcutaneously (under the skin) starting on day +7 after transplant to decrease the amount of time for white cells to grow.

Two medicines, cyclosporine and mycophenolate mofetil (MMF, Cellcept) will be used to prevent a complication of BMT called graft vs. host disease (GVHD). This is described in more detail below.

- 1) **Cyclosporine:** All subjects will receive cyclosporine IV starting day -1 (the day before transplant). This will be changed to **tacrolimus** (Prograf) by mouth before hospital discharge. We will begin to wean the tacrolimus starting at 100 days after transplant, unless you develop GVHD.
- 2) **Mycophenolate mofetil (Cellcept)** by mouth three times a day until day +45 after transplant.

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- 3) Unrelated cord blood: Will receive **methylprednisolone** IV (prednisone) starting 7 days after transplant until neutrophils (white cells) are greater than 1000.

Routine care: blood tests weekly (more often in the hospital) for blood count, kidney and liver function and viral studies until day 100 after transplant. After day +100, blood tests every 1-2 weeks until 6 months after transplant. If you are doing well, then blood tests every 2-4 weeks.

Engraftment tests (blood test), to test how many cells in the blood are from the donor: at approximately day 28, then monthly until 1 year from transplant, then at 2 years.

Special studies

Subjects with history of monthly transfusions:

- MRI of the liver (special image of the liver that can tell how much iron has accumulated from blood transfusions: before transplant and 2 years after.

Subjects with sickle cell disease:

- Previous stroke or abnormal transcranial Doppler (TCD): head MRI/MRA before transplant and 2 years after. MRI and MRA are special images of the brain and brain blood vessels.

HOW LONG IS THE STUDY?

You will be in the study for 2 years. Your doctor (the doctor taking care of you during your transplant, or your oncologist, or your primary care doctor) will follow you indefinitely and provide us with information as described above. Please notify your transplant doctor if you move or change your primary care doctor, so that we will be able to obtain all the information requested

WHAT ARE THE RISKS OF THIS STUDY?

The major risk of RIC is non-engraftment and graft loss. This may occur within 1-2 months following the transplant, or you may grow donor cells, and then lose them over several months. When non-engraftment or graft loss occurs, your original bone marrow generally re-grows, but the disease for which you were transplanted returns as well.

There have been reports of auto-immune hemolytic anemia occurring after RIC. This is a rare complication where the breakdown of red blood cells from antibodies causes anemia. The anemia may become severe enough that transfusions and other medicines may be necessary.

General risks of blood and marrow transplant are:

1. Infection: The immune system will be not be normal for many months, and the white blood cells that fight infection will be very low until the new blood cells grow. You will be taking antibiotics by mouth, to help decrease the possibility of infection, and you will be receiving intravenous gammaglobulin (IVIG), to help decrease the possibility of a serious viral infection. IVIG is given every 2 weeks for 3 months. We then follow your gammaglobulin levels to determine when and if you need additional infusions. If you should have a fever, intravenous antibiotics would be started. Usually, we are successful in treating a bacterial

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infection with antibiotics, but infection can be life threatening, and some subjects may die as a result of an infection. Other types of infections that can occur are from fungi or viruses. Viral infections can, in particular, be dangerous, as there are few antibiotics against most viruses.

2. GVHD: This occurs when the donor's white blood cells recognize the subject's body as "foreign". In acute GVHD, which occurs within 3 months of transplant, the skin, liver, or intestine may be affected. This may result in a rash, yellowness of the skin (jaundice) or very watery diarrhea. The donor blood cells will be specially treated to eliminate many of the T cells that cause GVHD, and the drug cyclosporine will also be given to help prevent GVHD. However, mild to severe GVHD may still occur. If GVHD should develop, it will be treated with other medications that have been successful in eliminating or controlling symptoms in many subjects. We are often successful in controlling acute GVHD with medicines, but not always, and fatal (deadly) complications may arise.

Chronic GVHD occurs most commonly in subjects who have had acute GVHD, but may occur in subjects who did not have any acute symptoms. It usually develops after the third month post transplant. It has been more common in subjects who have received peripheral stem cells or marrow that have not had T cells removed. Subjects can have problems with skin, liver, intestine, joints, mucous membranes, eyes, or other organs. Scarring may result. Medicines can help, but may not completely eliminate all the symptoms. Chronic GVHD may have lingering symptoms for years, or may go away completely. Infection is a major risk for subjects with chronic GVHD, as the immune system often does not return to normal.

3. Graft Rejection/Graft loss: This occurs when the subject's body does not accept the transfused donor blood or marrow cells. Graft rejection and graft loss are more common in reduced intensity transplants than in transplants which completely destroy the blood making cells. There is also an increase risk of graft rejection if you have Thalassemia Major, that is why your conditioning is slightly different. In addition, if you are to receive a cord blood product (transfusion) for your reduced intensity transplant, there is an increased risk of rejection. If this should occur, it may be possible to have another transplant with additional drugs and/or radiation.

4. Bleeding: As the platelets, which help blood clot, will be low until the new stem cells grow, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, we are successful in preventing major bleeding problems with transfusions of platelets. However, some subjects may not respond well to transfused platelets, and may be at serious risk for bleeding.

5. Veno-Occlusive Disease (VOD): This can occur as a result of drugs used for conditioning. Symptoms include jaundice (yellowness of the skin and eyes), with liver dysfunction, weight gain, and extra fluid in the abdominal cavity. It may often be managed successfully, and completely resolve. However, complications can arise that can be fatal.

6. Mucositis and diarrhea: The drugs used for conditioning may cause erosion in the lining of the mouth and intestines (mucositis). This can result in painful mouth sores and diarrhea. Pain medicine is generally required when mucositis is severe. Mucositis gets better when the white blood count starts to rise, and engraftment occurs.

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7. Capillary leak syndrome: This may occur as a result of drugs used for conditioning. The blood vessels may become “leaky” and fluid enters the abdominal cavity and tissues. A subject may gain water weight and the urine output may fall. Capillary leak syndrome can be difficult to manage, if extra fluid enters the lungs and causes difficulty breathing. Subjects may die if there is a continued fluid collection in the lungs.

8. Unexpected organ damage: It is possible that unexpected, life-threatening heart, lung, kidney, or liver damage may occur as a result of this therapy. You will be informed if problems arise and the measures being taken to help you. Rarely, multiorgan failure (such as lung and kidney failure) may occur, which almost always results in death, despite intensive care management.

9. Late Effects: These may include gland problems resulting in poor growth and sterility (inability to have children). However, the long term effects using RIC upon gland function (growth, reproduction) are less than with myeloablative conditioning regimens.

10. Risks of stem cell processing: The blood cells that have been collected will be brought to the Stem Cell Laboratory, and processed under sterile conditions. The risks to this procedure include contamination with bacteria and other agents and malfunction of equipment with a loss or decrease of stem cells. These risks are extremely small.

The risks of the individual drugs given as treatment are listed on the tables in Attachment #1.

Risks of Pregnancy

For Female Patients:

Females who are pregnant or nursing should not receive chemotherapy, radiation therapy, or many of the medicines used to treat the side effects of these therapies. The therapies we use to treat cancer are known to be very harmful to unborn children and can cause serious birth defects. Because of this, if you are at least twelve years old or have already started having periods, you will have a pregnancy test before starting any chemotherapy. For safety reasons, if you are found to be pregnant, you will not be able to start cancer therapy. The results of any pregnancy test done will be shared with you only, although we will encourage you to tell your parents. Counseling and other support will be provided.

You should not become pregnant while receiving cancer treatment. You need to take safety measures to prevent pregnancy (such as not having sexual intercourse, using condoms and taking birth control pills, using Depo-Provera, spermicides, or an intrauterine device (IUD), etc.). If you have questions about how to prevent pregnancy, talk to your doctor. You should tell your physician at once if you think you might be pregnant during your therapy.

For Male Patients:

You should not father a baby while on this study. The therapies we use to treat cancer are known to be very harmful to unborn children and can cause serious birth defects. You need to take safety measures to prevent pregnancy (such as not having sexual intercourse or using condoms and spermicides, etc.). If you have

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questions about how to prevent pregnancy, you are encouraged to talk with your doctor. You should you're your physician at once if you think you may have gotten someone pregnant during your treatment for cancer.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY

The possible benefits of a reduced intensity conditioning are fewer short-term toxicities of lungs, liver and heart, and less long-term side effects. The hospital stay is usually shorter than after conditioning that completely destroys the bone marrow, and blood counts may recover more quickly. In general, the benefits of your child's undertaking this transplant include possible cure of your child's primary disease. With your child's disease, conventional therapy with medicines or transfusions may prolong life, but is extremely unlikely to result in a cure.

DO YOU NEED TO GIVE YOUR CONSENT IN ORDER TO PARTICIPATE?

Once you understand the study, you will be asked to decide if you wish to participate. If you wish to participate in this study, you must sign this form. A copy will be given to you to keep as a record.

WHAT HAPPENS IF YOU DECIDE NOT TO TAKE PART IN THIS STUDY?

Your doctor will discuss other treatment options with you. These other options include continuing with conventional medicines or transfusions for your child's particular illness, or undertaking a fully myeloablative conditioning transplant.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

Please let us know if you have additional questions, please do not hesitate to call Dr. Timothy Olson at 267 426-5516. It is important that you understand the known hazards that might occur during therapy, and the possibility that all hazards might not be known.

WILL CONFIDENTIAL INFORMATION BE COLLECTED AS PART OF THIS STUDY?

We need to collect health information about you in order to conduct this study. This includes information about you from medical records and from the procedures, interviews and tests that are part of this research. 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 or published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation about the study. People and organizations that may inspect and/or copy your research records to conduct this research, assure the quality of the data and to analyze the data include:

- Members of the research team and other authorized staff at CHOP;
- 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 National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research, organizations involved in the coordination of this study;
- The National Heart Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.

By law, CHOP is required to protect your health information. 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. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is voluntary. You may choose not to take part or may withdraw from the study at any time before conditioning and transplant. Not participating or withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide that you will stop being in the study, please talk with the researcher or your doctor, so medicines can be stopped in the safest possible way.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

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You can decide to stop your participation at any time before conditioning starts. Tell your doctor if you are thinking about stopping or decide to stop. The doctor will tell you how to stop safely. It is important to tell your doctor if you are thinking about stopping so any risks from the medications can be evaluated. Another reason to tell your doctor is to discuss what follow-up care and testing could be most helpful for you.

You may change your mind and take back your authorization to use and disclosure your health information at any time. Even if you take back your authorization, we may still use and disclose the health information we have already obtained about you as necessary to maintain the integrity or reliability of the current research. To take back your authorization, you must send a letter to Dr. [Olson](#).

- In the letter, you must say that you changed your mind and do not want us to collect any more health information about you. If you ask that we no longer collect your health information you will have to leave the study.

If you decide to withdraw from the study or your doctor withdraws you from the study, we will ask your permission to use all the information about you that has already been collected as part of the study and to continue to allow your doctor to tell us about your progress until at least two years post-transplant. You can choose to grant or not to grant this permission.

CAN THE DOCTOR WHO IS THE PRINCIPAL INVESTIGATOR WITHDRAW YOU FROM THE THIS STUDY?

You can be taken off the study (with or without your consent) for any of the following reasons:

- You need a medical treatment not allowed in this study
- The investigator decides that continuing in the study would be harmful to you
- You become pregnant and the study treatment could be harmful to the fetus
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH)

WILL THERE BE ANY COSTS TO YOU?

Your insurance company must agree to reimbursement for the treatment and before hospital admission. If your insurance company does not agree to reimburse for the treatment, you have the option to cover the costs of the treatment yourself.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

WILL YOU BE PAID FOR TAKING PART IN THIS STUDY?

You will not be paid to participate in this study.

WHAT IF YOU HAVE QUESTIONS ABOUT THIS STUDY?

All of your questions should be answered before you consent to participate in this research study.

If you have further questions about the treatment, you may call Dr. Timothy Olson at 267 426 5516. If you have any questions about the rights of research subjects, you may call the IRB Office at 215-590-2830.

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If you are in the United States, you may call the NCI's *Cancer Information Service* at

- 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615
- Visit the NCI's *Web site* at <http://www.nci.nih.gov/cancerinfo/>
- Information about long term follow-up after cancer treatment can be found at <http://www.survivorshipguidelines.org/>
- You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).
- 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 THIS 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. Timothy Olson (267) 426-5516. 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.

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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

☐ Legal Authorized Representative

Signature of Authorized Representative

Date

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**Assent of Adults with diminished capacity to
Take Part in this Research Study**

For Adults with diminished capacity capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

Person Obtaining Assent

Signature of Person Obtaining Assent

Date

This study has been explained to me and I agree to take part.

Signature of Subject (optional)

Date

For adults with diminished capacity unable to assent:

I certify that _____ was not capable of understanding the procedures involved in the study sufficiently to assent to study participation.

Person Responsible for Obtaining Assent

Signature of Person Responsible

Date

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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
-
- ☐
- Legal Authorized Representative

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/legally authorized representative'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 or the adult's participation. They have also agreed to let CHOP use and share the health information as explained above. If they don't agree to the collection, use and sharing of the 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

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Date: _____

Assent of Adults with diminished capacity to Take Part in this Research Study (*Non-English Speaking Subjects*)

For adults with diminished capacity capable of providing assent:

I have explained this study and the procedures involved to _____ in terms he/she could understand and that he/she freely assented to take part in this study.

Person Obtaining Assent

Signature of Person Obtaining Assent

Date

For adults with diminished capacity unable to assent:

I certify that _____ was not capable of understanding the procedures involved in the study sufficiently to assent to study participation.

Person Responsible for Obtaining Assent

Signature of Person Obtaining assent

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 assent 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 assent 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 assent (including responses to the subject's questions) and responded affirmatively.

Name of Witness/Interpreter

Signature of Witness/Interpreter

Date:

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Attachment #1 Risks of Transplant

Specific risks of drugs used for transplant include:

CAMPATH:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving Campath, more than 20 may have:
• Chills • Fever • Nausea • Vomiting • Rash • Low blood counts • Severe infection • Pain
OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving Campath, from 4 to 20 may have:
• Low blood pressure • Fatigue • Hives • Itching • Shortness of breath • Headache • Diarrhea • Loss of appetite
RARE SIDE EFFECTS, AND SERIOUS In 100 people receiving Campath, 3 or fewer may have:
• Dizziness • Trembling • Fast heartbeat • Abdominal pain • Constipation • Difficulty sleeping

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BUSULFAN:**COMMON SIDE EFFECTS, SOME MAY BE SERIOUS**

In 100 people receiving Busulfan, more than 20 may have:

- Anemia which may require blood transfusions
- Abnormal heartbeat
- Constipation, diarrhea, heartburn, nausea, vomiting, loss of appetite
- Sores in mouth which may cause difficulty swallowing
- Chills, fever
- Pain
- Swelling of the body
- Damage to the liver
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Bruising, bleeding
- Dizziness, headache, tiredness
- Difficulty sleeping
- Worry
- Cough, stuffy nose
- Rash
- High blood pressure which may cause blurred vision
- High or low levels of certain salts in the body which may require you to take another medicine to correct the salt level

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Busulfan, from 4 to 20 may have:

- Cloudiness of the eye, visual disturbances
- Seizure
- Blood in urine
- Loss or absence of sperm
- Menopause
- Internal bleeding which may cause coughing up blood
- Scarring of the lungs

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Busulfan, 3 or fewer may have:

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RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Busulfan, 3 or fewer may have:

- Infection, especially when white blood cell count is low
- Fluid around heart
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Cancer of bone marrow caused by chemotherapy
- Low blood pressure which may cause feeling faint

FLUDARABINE:**COMMON SIDE EFFECTS, SOME MAY BE SERIOUS**

In 100 people receiving Fludarabine Phosphate, more than 20 and up to 100 may have:

- Infection, especially when white blood cell count is low
- Vomiting, loss of appetite
- Tiredness, fever
- Pain
- Bruising, bleeding
- Cough
- Increased risk of unusual infections lasting more than 6 months

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Fludarabine Phosphate, from 4 to 20 may have:

- Anemia, kidney problems which may cause tiredness, bruising, or swelling
- Nausea, chills
- Feeling of "pins and needles" in arms and legs
- Damage to organs which may cause tiredness, changes in thinking or shortness of breath
- Confusion

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Fludarabine Phosphate, 3 or fewer may have:

- Kidney damage which may require dialysis

HYDROXYUREA:**COMMON SIDE EFFECTS, SOME MAY BE SERIOUS**

In 100 people receiving hydroxyurea, more than 20 may have:

- Decrease in the number of red and white blood cells and platelets made in the bone marrow

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving hydroxyurea, from 4 to 20 may have:

- Nausea
- Vomiting
- Mouth sores
- Low number of red blood cells

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving hydroxyurea, 3 or fewer may have:

- Rash
- Redness of the skin on the face
- Painful and difficult urination
- Kidney damage
- Headache
- Dizziness
- Yellow-colored appearance of the skin and eye due to abnormal flow of bile
- Worsening of side effects due to radiation treatments
- Seeing or hearing things that are not really there
- Seizures
- Diarrhea
- Temporarily increased levels of liver enzymes
- Darkening of the skin
- Nail changes

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THIOTEPA:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS
In 100 people receiving Thiotepe, more than 20 and up to 100 may have:
• Nausea • Vomiting • Loss of appetite • A feeling of extreme tiredness or weakness • Fewer white blood cells, red blood cells and platelets in the blood. - A low number of red blood cells can make you feel tired and weak. - A low number of white blood cells can make it easier to get infections. - A low number of platelets causes you to bruise and bleed • Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children • Absence or decrease in monthly periods and could affect your ability to become pregnant • • With High Doses used before marrow transplants: • Inflammation and/or sores in the mouth, throat and/or esophagus (the passage between the throat and stomach)

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS
In 100 people receiving Thiotepe, from 4 to 20 may have:
• Pain at the injection site • Dizziness • Headache • Blurred vision • Hives, skin rash • Wheezing • Sudden high fever • Pain in the abdomen • Difficulty emptying the bladder

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OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Thiotepea, from 4 to 20 may have:

- Feeling the urgency to urinate or pain on urination
- Hair loss
- Inflammation and reddening of the eye
- Inflammation of the skin where the drug comes into contact with the skin
-
- With High Doses used before marrow transplants:
- Inappropriate behavior
- Confusion
- Drowsiness
- Elevation in the blood of certain enzymes and/or bilirubin found in the liver
- Bronze discoloration or darkening of the skin

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving thiotepa, 3 or fewer may have:

- Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
- Swelling and tightening of the throat which can cause difficulty with breathing
- A new cancer or leukemia resulting from this treatment

MELPHALAN (intravenous)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Melphalan, more than 20 and up to 100 may have:

- Sores in mouth which may cause difficulty swallowing

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Melphalan, from 4 to 20 may have:

- Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis or require blood transfusions
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Hepatitis which may cause yellow eyes and skin, tiredness
- A new cancer resulting from treatment of earlier cancer
- Cancer of bone marrow caused by chemotherapy

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OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Melphalan, from 4 to 20 may have:

- Kidney damage which may cause swelling, may require dialysis
- Scarring of the lungs which may cause shortness of breath

RARE, AND SERIOUS

In 100 people receiving Melphalan, 3 or fewer may have:

- Heart stops beating
- Swelling and redness at the site of the medication injection
- Abnormal or absence of menstrual period, menopause
- Loss or absence of sperm

MYCOPHENOLATE (CELLCEPT)
COMMON, SOME MAY BE SERIOUS

In 100 people receiving Mycophenolate (Cellcept), more than 20 may have:

- Diarrhea
- Stomach pain
- Nausea
- Difficulty falling asleep or staying asleep

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Mycophenolate (Cellcept), from 4 to 20 may have:

- Pain in back, joints and muscles
- Constipation

RARE, AND SERIOUS

In 100 people receiving Mycophenolate (Cellcept), 3 or fewer may have:

- Swelling of the hands, feet or lower legs
- Difficulty breathing
- Shaking hands
- Headache
- Fast heartbeat
- Tiredness, Dizziness
- Blood in stools
- Gum swelling
- Vision changes
- Rash
- Low blood counts

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CYCLOSPORINE A/ TACROLIMUS**COMMON SIDE EFFECTS, SOME MAY BE SERIOUS**

In 100 people receiving Cyclosporine A/ tacrolimus,
more than 20 and up to 100 may have:

- Headache
- Nausea and vomiting
- High blood pressure
- Loss of desire to eat or appetite
- Reduced ability of the body to fight infection
- Diarrhea or constipation
- Fever
- Tremor (shakiness usually of the hands)
- Increases in the levels of certain chemicals in the blood because the kidney is not working as well as normal which may require lowering the dose
- Fewer red blood cells in the blood
 - a low number of red blood cells can make you feel tired and weak
- Difficulty sleeping or falling asleep
- A feeling of weakness and/or tiredness
- Pain which may be in the abdomen (belly), back and/or other parts of your body
- High levels of sugar in the blood that may require treatment
- Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or vein
- Low (*or High*) levels of certain salts in the body like potassium and phosphate which may require treatment
- Numbness and tingling in the fingers and toes

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus, from 4 to 20 may have:

- Chest pain
- Hair loss
- Dizziness
- Elevation in the blood of certain enzymes or bilirubin found in the liver which may mean the liver is not working as well
- Bladder or kidney infection
- Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight
- Rash that may itch
- An increase in the levels of lipids (fats) and cholesterol in your blood which if prolonged could lead to heart problems later in life

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OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus, from 4 to 20 may have:

- Acid or upset stomach (heartburn)
- Difficulty or discomfort on swallowing
- Inflammation of the stomach or esophagus (the tube that leads from the mouth to the stomach)
- Too much gas produced in the intestines
- Shortness of breath and/or a tight feeling in the chest with wheezing and shortness of breath (asthma)
- Increased cough
- Flu type symptoms with fever, tiredness, aches and pains
- Changes in your brain function such that you have difficulty in thinking clearly, are sleepy, depressed, anxious, have strange dreams, are nervous, have changes in your mood which may include severe depression, feelings of suicide, feelings of aggressiveness and violent behavior or see or hear things that are not there
- Fewer white blood cells and platelets in the blood
- a low number of white blood cells can make it easier to get infections
- a low number of platelets causes you to bruise and bleed more easily
- Greater than normal numbers of white or red blood cells in the blood
- Aches and pains in the joints or muscles
- Skin changes including pimples, change in color, increased tendency to sun burn and skin sores
- Wounds may be slower to heal
- Excessive hair growth such as on the face, eyebrows, arms and legs
- Bleeding or tender gums, overgrowth of gum tissue
- Changes in your vision or a decrease in vision
- Ear pain or ringing in the ears
- Gallstones

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus,
3 or fewer may have:

- Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
- Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen which makes it look larger.
- Inflammation of the lungs which could lead to chest pain and discomfort
- A new cancer or leukemia resulting from this treatment

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FILGRASTIM (G-CSF):**COMMON SIDE EFFECTS, SOME MAY BE SERIOUS**

In 100 people receiving filgrastim (G-CSF), more than 20 may have:

- Nausea, vomiting
- Pain in bone

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving filgrastim (G-CSF), from 4 to 20 may have:

- Anemia which may cause tiredness, or may require transfusion
- Damage to the lungs which may cause shortness of breath
- Internal bleeding which may cause coughing up blood
- Swelling or tenderness of vessels

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving filgrastim (G-CSF), 3 or fewer may have:

- Rupture of the spleen leading to bleeding in the belly