

PRINCIPAL INVESTIGATOR: Dimana Dimitrova, M.D.
STUDY TITLE: Phase II Trial of Allogeneic Hematopoietic Cell Transplantation for Disorders of T-cell Proliferation and/or Dysregulation
STUDY SITE: NIH Clinical Center

Cohort: *Recipient*
Consent Version: *07/16/2024*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Dimana Dimitrova, M.D. by phone at 240-858-3647 or email: dimana.dimitrova@nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being enrolled is a minor then the term “you” refers to “you and/or your child” throughout the remainder of this document.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term “you” refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This study is being done to evaluate a lower toxicity way to treat patients with T cell problems who need allogeneic blood or marrow transplant. The study aims to determine if allogeneic blood or marrow transplant can be made more effective in patients with T cell problems while also minimizing side effects and complications.

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

You are being asked to take part in this study because you have a problem with your immune system that may be corrected and perhaps even cured with transplantation. To be eligible, you must have abnormal T cell function that has caused significant health problems, such as serious infection, cancer, autoimmunity, or other problems with the immune system.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 177 people (117 recipients and 60 donors) will be screened on this study. However, not everyone that is screened will be eligible. It is expected that about 40 people will receive transplants on this study.

DESCRIPTION OF RESEARCH STUDY

Hematopoietic cells are immature cells that grow in the bone marrow and make all of the cells needed for blood production (red blood cells, white blood cells, and platelets) and for normal immunity, the body's defense against infections, cancers, and other insults. When these cells are taken from one person (called the "donor") and given to another person (called the "recipient"), it is called an allogeneic hematopoietic cell (blood stem cell and immune cell) transplant. Hematopoietic cells are collected for transplantation by taking either blood or bone marrow from the donor. These cells are then given to the recipient through a catheter (plastic tube) in the veins. When transplants are successful, these cells make their way to the bone marrow and start making the blood cells and immune system cells for the recipient. Transplantation has been used successfully to cure many kinds of immune diseases, cancers, and diseases of the blood. The reason for transplant in this study is to provide a new, healthy immune system to correct the immune problems in the recipient.

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

Before you begin, the following will be performed to determine if you are eligible to participate. If you have had some of these tests or procedures recently, they may or may not have to be repeated:

- Review list of your current medications, relevant medical records, and potentially biopsy slides
- Physical exam to include height, weight, blood pressure, heart rate
- **Blood Draws (3 tablespoons):** Blood will be drawn from either an arm vein or a central venous access device if you have one. Routine blood tests to check your organ function, blood counts, immune system function, past exposures to infections, and screen for active infections and other routine tests that determine whether you meet the requirements for participating in a specific protocol.
- **HIV Testing:** As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

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- Pregnancy Test: For individuals who could have children, a pregnancy test will be done (blood or urine sample). You will not be able to participate if you are pregnant.
- Urine collection to screen for infection and measure kidney function
- Pulmonary Function tests; we will measure how well your lungs work. You will blow into a tube that is connected machine. You may be required to hold your breath at times and/ or blow really hard.
- Echocardiogram: An echocardiogram is used to evaluate the structure and function of your heart. It uses harmless sound waves which bounce off the heart structures as a series of echoes. The echoes are recorded on moving graph paper or a videotape.
- Blood and immune system typing for donor selection/matching
- Bone marrow aspiration and biopsy. Your hipbone will be numbed with a local anesthetic called lidocaine. A small cut will be made in the skin and a needle will be inserted into the hipbone. Liquid samples (aspiration) of the bone marrow will be removed through the needle. A small fragment of bone will also be removed with the needle. After the procedure, the biopsy site will be covered with a small bandage – stitches are not needed to close the small cut. This procedure will help the transplant team evaluate the health of your bone marrow and provide information to guide the decision about how much chemotherapy you will need to prepare your marrow for the transplant (low or medium “prep”).
- Assessment of central venous (intravenous line) access potential

First, we will confirm that you have dysregulated function of the T cells which make up part of your immune system by reviewing your history of infections, cancers, and other medical illnesses, as well as the results of blood tests, and past biopsies.

Next, we will determine if you have at least a half-matched related (family) donor or unrelated partially to fully matched donor who is medically fit and willing to donate. Approximately 5-10 tablespoons of blood will be drawn to test your blood type and immune system type so we can find the best match.

Before you begin the study therapy

After you have been screened and determined eligible, additional evaluations will be performed which include:

- Electrocardiogram (ECG): An electrocardiogram (ECG) is a test that is performed while you lie still for about 5 minutes. It involves placing electrodes (small stickers that are attached to wires that go to the machine) on the chest and arms/legs and recording the electrical activity of your heart. If you have a lot of hair on your chest, it may hurt a little bit when they remove these stickers.
- Additional blood tests to evaluate your endocrine system (hormone system), blood cells, infections, and immunity (about 6 tablespoons will be collected)

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- Dental consultation to evaluate the need for tooth cleaning or extraction prior to transplant
- Assessment of your nutrition by a dietician
- Meeting with a social worker
- Collection of research specimens (blood, bone marrow, and urine)

Some of these studies may already have been done during screening and may not need to be repeated. If you have signed the consent for and are co-enrolled in another NIH protocol that permits the sharing of identifiable data, then data that is collected on that study may be shared with and used for research in this study, so that you do not have to repeat these procedures/tests. If you agree to participate in this study, identifiable data that is collected as part of this study may be shared with and used for research in the study on which you are co-enrolled.

The Central Venous Catheter

If you do not already have one before you enroll in this study, you will receive an intravenous (I.V.) line called a central venous catheter that can be used throughout your transplant procedure and follow-up treatment. It will be used to give you all of study medications and can also be used for drawing blood samples for tests. Since blood will be drawn often during your treatment the catheter will make it easier and less painful. Most of the blood will be used to check on your health during and after your treatment. Some blood will be drawn for research. Your catheter will be placed in the upper part of your chest and tunneled under the skin into a neck vein. If the catheter becomes infected or clogged, it can be replaced. It will be flushed once daily to prevent clogging. The nursing staff may teach you how to do this yourself.

During the study therapy

After the above evaluations are complete, the transplant team will decide what intensity of conditioning or “prep” your bone marrow will need to prepare for transplant. The conditioning is chemotherapy given in the 2 weeks leading up to the day of transplant. In this study, we will not use radiation or very high levels of chemotherapy in the “prep”, so you will receive either medium or low intensity “prep”. If you are receiving the “low prep”, you will receive chemotherapy on days -9 through -2. If you are receiving the “medium prep”, you will receive chemotherapy on days -11 through -2. Prior to chemotherapy, for either the “low prep” or “medium prep”, you will receive antibody therapy on days -14 and -13. The antibody therapy is horse anti-thymocyte globulin (ATG), an antibody that attacks certain white blood cells, particularly T cells. This antibody will help clear parts of your immune system to prepare for the transplant. All patients will receive both antibody therapy and chemotherapy as part of their “prep”. Most patients will remain hospitalized until around four weeks after the transplant, although this may vary depending on if there are complications.

You will be hospitalized starting on the day prior to the start of the antibody therapy (day -14), if not earlier to complete pre-transplant evaluations, tests, and procedures.

Before your transplant, you will have a central venous catheter put into a vein in your chest or neck. Medications and transfusions can be given through the catheter and blood can be drawn off

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the catheter during your transplant. This should make blood draws easier and less painful. On average, you will have approximately between 3 and 4 tablespoons of blood collected at each timepoint. At each yearly follow up visit, you will have approximately 6 tablespoons of blood collected. There is a chance that the catheter can become infected, clogged, or move out of the correct position. In these cases, it may be able to be fixed, treated, or may need to be replaced. You or your caregiver will be responsible for caring for the catheter if you continue to need it once discharged from the hospital. The nursing staff will teach you how to care for the catheter.

If you are receiving the “medium prep”, you may receive a small test dose of one of the chemotherapy medications (busulfan) to see how quickly your body breaks down the drug. This will determine the dose of busulfan that you will receive during your conditioning or “prep”. Real time pharmacokinetic samples (at total of 1 ½ tablespoons of blood) for busulfan may be drawn during conditioning in place of the test dose.

On the day of your transplant, you will receive the donor hematopoietic cells through the central venous catheter.

The role of a healthy immune system is to attack foreign invaders like bacteria or other infections, or to recognize and kill cells that have “gone bad”, like cancer cells. Sometimes, the donor immune system can see your body as “foreign” too. Starting on day 3 after your transplant, you will receive medicines to prevent graft-versus-host disease, which is when the donor immune system attacks your body (usually the skin, liver, and/or gut) as if it is a foreign invader or bad cell. These medications will include a chemotherapy drug called cyclophosphamide, as well as medications (tacrolimus and mycophenolate mofetil) that lower the immune system. You will receive cyclophosphamide on day 3 and day 4 after transplant. You will also continue one of these medications for a few weeks after transplant (mycophenolate mofetil) and one of these medications for several months after the transplant (tacrolimus). If you do not develop graft-versus-host disease, these medications will be stopped at designated time points after transplant. If you develop graft-versus-host disease, you may need additional medications. A study doctor will discuss these medications with you, if they become needed.

You will also take several medications to prevent infection after transplant. These are important to try to protect you from infections that can occur while your new immune system is gaining its function and skills in recognizing and fighting infection. You will be given a daily shot after transplant until your white blood cell count comes up to near normal numbers.

You will need to remain in the hospital for several weeks after your transplant. You will likely need transfusions of red blood cells and platelets in the early days after your transplant until the donor cells start making red blood cells and platelets of their own. You may have a fever, throat pain, tiredness, lack of appetite, hair loss, skin changes, and/or other health issues arise during your transplant. You will be monitored closely for changes in your organ function, blood counts, or for signs of infection. You may need procedures, radiology scans, additional medications, or blood tests, apart from those routinely scheduled, if issues arise before, during, or after your transplant.

From around day +30 through day +100 after transplant, patients who have been discharged from the hospital will be seen at least once a week in the NCI Oncology Clinic or day hospital.

From around day +120 on, most patients will be allowed to return home. Patients will need to return for follow-up visits to the NIH, which are at minimum around day +180, 1 year after

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transplant, 18 months after transplant, and then yearly from the 2-year mark on. The study ends when you reach 5 years after transplant.

During the study, blood, marrow, and urine specimens will be collected for research studies. These research studies will evaluate how your immune system works before, during, and after the transplant. The research studies will also evaluate how well your immune system (before and after transplant) controls common viruses that infect most people and remain in our bodies for the rest of our lives. The studies will also look for markers in the blood of graft-versus-host disease. You will not have to undergo additional procedures (such as a bone marrow biopsy) for us to collect these research samples. They will be collected when you are undergoing these procedures as part of your medical care. Research samples will be collected at scheduled times before, during, and after your transplant. Should a situation arise where non-scheduled research samples would be helpful to better understand your condition, you will be asked if you would be willing to have additional research samples collected. We may also collect urine and stool research samples from you if you have these types of samples collected as part of your clinical care. The information gained from these research studies will not directly benefit you but will hopefully lead to a better understanding of transplant and diseases of the immune system that will help patients like you in the future.

When you are finished taking the drugs (treatment)

Once you no longer need frequent infusions of medications through the central venous catheter, transfusions, and nursing care and you are strong enough to carry out your daily activities on your own, you will be discharged from the hospital. The average time in the hospital is 4-8 weeks, although this can vary based on the type of “prep” that you get and if there are complications. After discharge from the hospital, you will be required to remain in the Washington, D.C. area for approximately three months after transplantation. You may require readmission to the hospital if there are complications. You will be followed closely in the NCI clinic for the first six months after transplant, and then you will be followed less frequently for up to five years. You will also need to have a doctor near your home who can follow you regularly once your visits at NIH become less frequent.

After the transplant, you will be regularly evaluated for graft-versus-host disease, infections, and other possible complications of transplant. You will continue to need frequent blood draws and will likely require adjustments in your medications. You may be asked to fast (not eat) prior to some blood draws.

In the weeks after the transplant, we will also do blood tests to see how many of the white blood cells are coming from the donor immune system and how many are coming from your old immune system. This is one way that we measure the function of the donor cells in your body. If there are fewer donor cells than expected after transplant, you may need additional infusions of donor cells to improve the numbers. A bone marrow aspiration and biopsy will also be performed about 1 year after your transplant to evaluate the health of the bone marrow and the new immune system.

During the study, you will have blood, bone marrow, and urine specimens drawn for research to study how your immune system recovers after the transplant. The maximum amount of blood taken from you is based on your age and weight and will not be more than a strict volume limit set for research by the NIH. If you are age 18 or older, the amount of research blood collected will not

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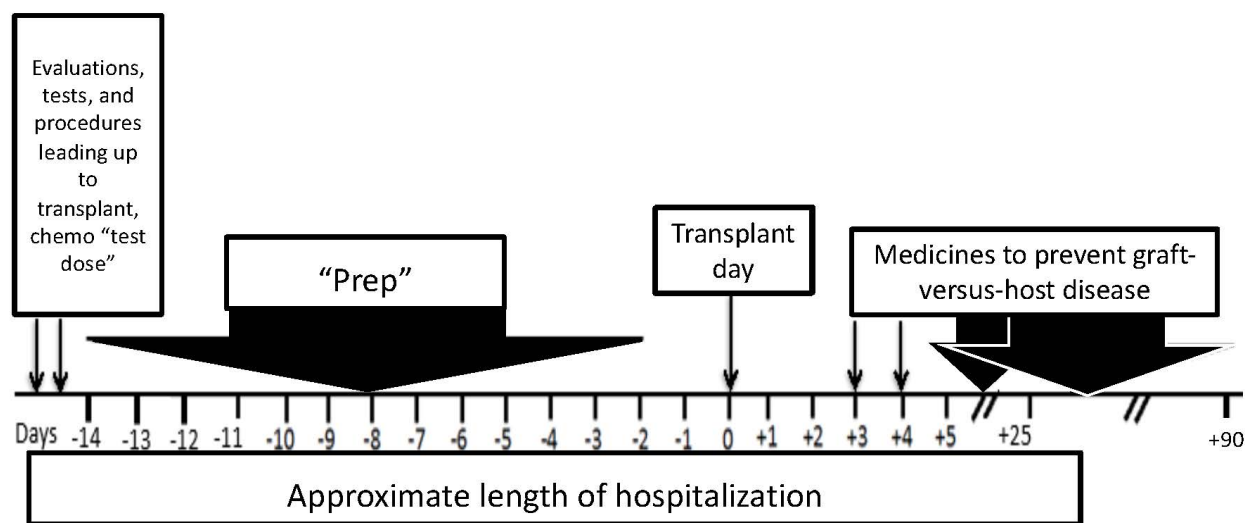
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exceed about 37 tablespoons (550 mL) over an 8-week period. If you are under the age of 18, the amount of research blood collected will not exceed about half a tablespoon (9.5mL)/kg over an 8-week period.

After your transplant, you will need to be re-vaccinated against infections. These vaccinations will start roughly 6 months after transplant, with delays possible depending on if your immune system is ready to handle the vaccines or not.

STUDY CHART

The following picture shows a general outline of the events that will occur in the weeks leading up to transplant through the three months after transplant.



BIRTH CONTROL

If you are a individual who is nursing or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 12 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

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RISKS OR DISCOMFORTS OF PARTICIPATION

Risk of death from transplant: Patients undergoing transplant are at risk of dying from the transplant procedure and its possible complications. Historically, there is about a 40% chance of death from complications of conventional allogeneic blood or bone marrow transplants. In this study, we are using new approaches to try to reduce these odds and make transplants safer. However, it is possible that our approach may be associated with similar chances of death. In transplant studies that are in some ways similar to the current study's approach, the risk of death in the first year after transplant is around 10-15%. The risk of death or other complications can vary greatly, depending on the age of the patient, the way the transplant is performed, the health of the patient at the time of transplant, and other factors. There is also a risk of complications that cannot be predicted.

Risk of acquiring a primary immunodeficiency, allergy, or other immune-system problem from a donor: Although possible, it is highly unlikely that you might acquire a primary immunodeficiency from a donor. All donors are screened for signs of immunodeficiency. If you have a related donor and a known mutation causing your immunodeficiency, that donor will be tested for your mutation. If a donor is found to have a primary immunodeficiency, they will not be used as donor. It is possible to acquire allergies, such as drug, food, or environmental allergies, from your donor. Donors are asked about serious or significant allergies, but they may not be aware of all of their allergies. This is particularly true for drug allergies, as donors are often exposed to very few drugs by nature of their good health. If a donor does have a significant drug allergy, we generally avoid giving you that family of drugs after transplant. It is also possible that other immune system problems could be acquired from your donor, such as autoimmune problems. We screen donors by asking them extensive questions about significant autoimmune problems and do not use donors who have known autoimmune problems that interfere with their health.

Risk of bone marrow aspiration and biopsy: This procedure usually causes only mild pain for a short time at the biopsy site. Very rarely, bleeding or infection may occur at the biopsy site.

Risk of blood draws: Blood will be drawn frequently during your evaluations and treatment. Most of the blood draws will be to monitor your health during and after the chemotherapy and transplant procedure. In addition, some blood samples will be drawn for research purposes. These samples will be used to study how your immune system is affected by the transplant.

Echocardiogram: An echocardiogram is an ultrasound to evaluate your heart structure and function. This test is very safe and is performed using a probe with gel placed on your chest.

Electrocardiogram (ECG): An ECG is a tracing of your heart rate and rhythm. This test is very safe and is performed using wires that are briefly placed on the skin of your chest.

Pulmonary (lung) function testing: These tests measure how well your lungs work. They are usually safe for most people. However, because the test may require you to breathe in and out quickly, you may feel dizzy. There's a small risk that you might faint. If you have asthma, this test could cause you to have an asthma attack. In very rare cases, pulmonary function tests may cause a collapsed lung. If you have asthma or feel lightheaded during the test, tell your doctor.

Collection of urine and stool samples: There are no risk related to stool or urine collection.

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Risks of central venous catheter: Side effects of placing a central venous catheter in your chest include bleeding, blood clots, or pain in the area of insertion. The line will be placed by physicians experienced in this procedure. These physicians will discuss the above risks at the time of placing the catheter. Rarely, placement of a central venous catheter can result in a collapsed lung. If a collapsed lung occurs, this may require hospitalization and temporary insertion of a plastic tube in your chest to re-expand the lung. Once the central venous catheter is in place, risks include infection, blood clot, and catheter malfunction. The catheter may need to be removed if one of these complications occurs. If you still require use of a catheter, another central venous catheter may need to be placed.

Risk of infection: The most common complication after transplant is infection. This includes issues with viruses, bacteria, fungus, and other infections. If you have active infections at the time of transplant, there is a risk that these infections may worsen, particularly in the early days of transplant. Even though you are receiving a transplant to improve your immune system, this improvement does not happen immediately, even if the transplant is completely successful. Even without any complications, the new immune system will take months to years after transplant to work normally. You will also be receiving chemotherapy and medications to prevent graft-versus-host disease that will decrease your immune system's ability to fight infection. You will be monitored closely for infection and treated if there are effective therapies. There are some infections that can occur after transplant that lack effective therapies.

Risk of infertility: This treatment may result in the inability to have children in the future. The risk of infertility is higher for patients who received chemotherapy in the past, prior to the transplant, or who enter into transplant with low fertility, for whatever reason. Other factors may impact your fertility after transplant, and these are difficult to predict for each patient. If you are interested in being evaluated by a reproductive endocrinologist to discuss fertility preservation prior to transplant, we can provide information about this process, but we do not have full fertility preservation services at the NIH. There is almost always a cost to the patient to undergo fertility preservation and store eggs or sperm. It is unknown what effects the chemotherapy, transplant procedure, and medications used in this study may have on an unborn child, but they would most likely be harmful. When participating in this study, you will be asked to agree to use birth control through one year after transplant.

Risks of antibody therapy: ATG is produced by the immune system of horses, so humans (particularly those who are allergic to horses or who have received the drug before) can have severe or life-threatening allergic reactions. Another possible complication is serum sickness, which feels like having the flu. This occurs when your own immune system tries to clear the horse antibody and deposits complexes of your antibodies bound to the horse protein in the muscles, skin, and joint tissues. Patients can have flu-like symptoms with joint aches, fever, and skin rash 7-12 days after starting the ATG therapy, without permanent side effects. Steroids and antihistamines are used to prevent and treat both allergic and serum sickness reactions. You will be given steroids at least days -14 through -7, if not for longer.

Risks of chemotherapy: Treatment with busulfan, pentostatin, and cyclophosphamide will reduce your white blood cell count and increase your risk of infection. Such infections can be very serious and may result in death. If you develop signs or symptoms of an infection, you may need additional blood tests, radiology tests, interventions, medications, and hospitalization. The chemotherapy

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drugs will also make your platelet count fall, which increases your risk of bleeding or bruising. If your platelet count becomes very low, you will receive platelet transfusions. The chemotherapy drugs will also make your red blood cell count fall, called anemia. Anemia can lead to lack of energy and other symptoms. Transfusions of red blood cells are often needed to treat anemia associated with chemotherapy and transplant.

Risk of hematopoietic cell infusion: The donor cells will be infused through your central venous catheter and will appear very similar to a blood transfusion. Some patients may develop a fever, chills, body aches, trouble breathing, anemia, or dark urine during or after the cell infusion. This does not mean that your body is rejecting the graft. These side effects usually occur because of other cells and proteins, apart from the hematopoietic cells, that react with your body. The infusion may need to be slowed down or held for a short time but will ultimately be infused completely. It would only be in the extremely rare circumstance where the infusion is deemed medically unsafe to continue that the cell infusion would not be completed, although this is not anticipated to occur.

Risk of graft rejection: In the first 2-4 weeks after transplant, nearly all patients will have very low blood counts. Engraftment – when the donor’s cells start making blood cells for you – usually occurs between days +16 and +28 after transplant. There is a chance that you may reject your donor’s cells. If that were to happen, you would most likely recover your own blood cells. If your own cells do not recover, this increases your risk of infection, bleeding, and death. During this time, we would attempt to support you with transfusions, growth factors, and antibiotics. If you have graft rejection, you may need another transplant or another infusion of donor cells.

Risk of Sinusoidal Obstructive Syndrome (SOS): A severe liver complication known as SOS occurs in less than 5% of allogeneic blood or marrow transplants. SOS is a chemotherapy side effect that causes the blood vessels of the liver to be blocked. The risk of SOS in this study is expected to be low. The highest risk is for patients who receive the high prep. Other factors such as prior liver disease may increase the risk of SOS. Severe SOS can lead to liver failure and death.

Risk of nutritional decline: Going through transplant is a time of high calorie and high protein needs for your body. Despite these high needs, you may feel unwell and may be unable to keep up with the high energy demands on your body. This can lead to weight loss, muscle mass loss, and nutritional deficiency. These issues are usually temporary. You will receive evaluation by a dietician throughout your transplant course to assist in finding ways to meet your body’s energy demands during transplant and minimize the risk of nutritional decline.

Risk of Graft-versus-Host Disease (GVHD): You will be at risk for the development of GVHD for the rest of your life after transplant. There are two forms of GVHD – one that typically occurs earlier after transplant called “acute GVHD” and one that occurs typically later after transplant called “chronic GVHD”. Acute GVHD most commonly attacks the skin, liver, and/or gut. Symptoms of skin GVHD may be as mild as an itchy rash or as severe as blistering and loss of the skin. Symptoms of gut acute GVHD may be as mild as heartburn, nausea, or mild diarrhea, or as severe as cramping abdominal pain and large volumes of diarrhea. Liver acute GVHD may be as mild as a slight disturbance in liver function, or as severe as jaundice (yellowing of the skin) with liver failure. Mild acute GVHD can be treated with steroid creams applied to your skin. Severe GVHD can be very dangerous and needs to be treated aggressively. Treatment of severe acute GVHD included weakening the immune system with steroids and other medications. This can increase your risk of infection, cancer, and death. Chronic GVHD, if it occurs, typically appears

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later after transplant. Some degree of chronic GVHD affects about half of patients after conventional transplant. With the approach used in this study, the risk of chronic GVHD is much lower, likely less than 15%. Chronic GVHD commonly attacks the skin, eyes, mouth, liver, or intestines, but can also involve the lungs, muscles, joints, bone marrow, and other organs. Symptoms of chronic GVHD may include dryness of the mouth or eyes, loss of appetite, weakness, hair loss, changes in skin color or texture, liver damage, weight loss, shortness of breath, cough, or other symptoms. Patients with severe chronic GVHD are also at increased risk of infection or death. Chronic GVHD is also treated with drugs to weaken the immune system, such as steroids. Taking steroids increases your risk of infection, bone thinning, diabetes, cataracts, weight gain, and other complications.

Risk of late transplant complications: There are other potential complications that can occur long after transplant. These could affect any organ in the body and are usually due to late effects of damage done by chemotherapy or other medications used for transplant. Rarely, transplant patients are at risk for developing cancer. However, most patients with primary immunodeficiency are at increased risk of cancer and it is estimated that the risk of cancer will decrease if the transplant is successful.

Risk of failure of the transplant to correct the immune system: There are many different types of primary immunodeficiencies, each with a unique problem in the cells of the immune system. You will only be eligible to participate in this study and receive a transplant if it is felt that the donor cells have the potential to reverse the problems with your immune system. However, each primary immunodeficiency is different, and it is difficult to predict how quickly or effectively the donor cells will improve your immune system. We will closely monitor the function of your immune system before and after transplant. More donor cells can be given after the transplant if it appears that more cells are needed to boost up your immune system function. With the transplant, only blood cells are being replaced. This means that non-blood cells in your body that are directly affected by your disease will likely not be fixed by the transplant.

Risk of complications related to your underlying immunodeficiency: With your underlying immunodeficiency, there may be parts of your body that are vulnerable to complications. Transplant has the potential to worsen these vulnerabilities. As examples, patients with immunodeficiency may have a tendency towards poor wound healing, thin bones and risk of fracture, gut inflammation with diarrhea or bleeding, etc. The process of transplantation may increase the risk of these potential complications occurring or worsening. We hope that transplant will ultimately improve your overall health, but it is important to understand that transplant is not without risk. We will counsel you prior to transplant regarding particular issues related to your immunodeficiency that we anticipate may have the potential to occur or worsen, reversibly or permanently, during the transplant process.

Risk of cancer relapse after transplant: If you have lymphoma as your reason for transplant, there is a risk of lymphoma relapse after transplant. While it is hoped that transplant will cure the lymphoma, this does not happen for all patients. If your lymphoma relapses after transplant, you may require additional therapies to try to treat the lymphoma. These therapies may be able to be given on this study, another study at the NIH, or may require you to return to your community oncologist for further treatment.

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Risk of bleeding in patients with MagT1 mutation (XMEN): There may be increased risk of serious bleeding for patients who have a MagT1 mutation during transplant, even if the patient has not had serious bleeding before. Patients with MagT1 mutation will be evaluated more extensively prior to transplant to better assess bleeding risk and will likely receive more platelet transfusions after transplant than other patients. Patients with MagT1 mutation will need to not take any medications that could thin the blood or hinder platelet function while their platelet count is low during transplant.

What side effects or risks can I expect from being in this study? The potential side effects or risks of the main drugs used in this study are listed separately below. You will receive other drugs, not listed here, as part of the supportive care to help you through transplant and minimize complications. These drugs are not experimental. These include antibiotics, medicines to protect the liver, and medications to address issues like pain, nausea, diarrhea, allergic reactions, fever, or other discomforts associated with the transplant. For all drugs, there is a potential for a serious allergic reaction. You may not receive all of the drugs listed below, or you may receive doses of the drug that make the side effects listed less likely than outlined below.

ATG (all patients):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> Fever Chills Skin rash Low blood counts 	<ul style="list-style-type: none"> Chest pain Diarrhea Nausea Vomiting Back pain Abnormal kidney function Serum sickness (feeling “flu-like”) Shortness of breath Sepsis (serious infection requiring intensive monitoring and treatment) 	<ul style="list-style-type: none"> Anaphylaxis (severe allergic reaction with tongue/throat swelling/trouble breathing) Pulmonary edema (fluid in the lungs)

Prednisone (all patients):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> Trouble sleeping High blood sugar Increased appetite Fluid retention 	<ul style="list-style-type: none"> Irritable mood High blood pressure Stomach ulcers Easy bruising 	<ul style="list-style-type: none"> Damage to the bones (avascular necrosis) Cataracts (clouding of the eye lens)

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Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Infection 	<ul style="list-style-type: none"> • Trouble with wound healing • Abnormal liver function • Allergic reaction 	<ul style="list-style-type: none"> • Glaucoma (high pressure in the eye) • Nerve damage or muscle weakness

Pentostatin (all patients):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Infection • Nausea/vomiting 	<ul style="list-style-type: none"> • Skin rash • Allergic reaction 	<ul style="list-style-type: none"> • Damage to the central nervous system causing seizures, coma, or even death • Inflammation of the lungs • Kidney damage

Cyclophosphamide (all patients):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Low blood counts • Hair loss 	<ul style="list-style-type: none"> • Nausea/vomiting • Painful urination and/or blood in the urine • Sterility • Water retention • Burning or congestion in the sinuses • Headache • Diarrhea 	<ul style="list-style-type: none"> • Heart damage • Secondary leukemia • Retention of too much fluid in the body • Pulmonary fibrosis (lung scarring)

Busulfan (for “medium prep” patients only):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Low blood counts • Hair loss 	<ul style="list-style-type: none"> • Nausea/vomiting • Skin rash • Headache • Sterility 	<ul style="list-style-type: none"> • Secondary leukemia • Pulmonary fibrosis (lung scarring) • Liver damage

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Likely	Less Likely	Rare but Serious
		<ul style="list-style-type: none"> Seizures

Mesna (all patients):

- At the doses used in this study, mesna is virtually non-toxic with minimal to no anticipated side effects.

Tacrolimus (all patients):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> Headache Tremor Changes in mental status High blood pressure Abnormal kidney function Constipation Diarrhea Abdominal pain Difficulty sleeping (insomnia) 	<ul style="list-style-type: none"> Changes in liver function tests Diabetes Anemia Allergic reaction Sensitivity reaction to light 	<ul style="list-style-type: none"> Seizure Coma

Mycophenolate Mofetil (all patients):

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> Neutropenia Anemia Indigestion Nausea Diarrhea Risk of infection 	<ul style="list-style-type: none"> Acne Rash Itching 	<ul style="list-style-type: none"> Secondary cancers

Filgrastim (all patients):**PATIENT IDENTIFICATION****Consent to Participate in a Clinical Research Study**

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Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none">Pain at the needle site	<ul style="list-style-type: none">HeadacheBone painFeversTiredness	<ul style="list-style-type: none">Rupture of the spleen

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The transplant may improve the chance that your immune system will function more normally. There is the chance that transplant can cure your disease. If your immune system functions normally, it is possible that you would have fewer or less serious infections, lower risk of cancer, and need fewer medications to support your immune system and prevent infection. However, you should understand that this cannot be guaranteed. In addition, your participation in this experimental study may contribute to understanding and developing new ways of using transplant for the treatment of immunodeficiencies. Knowledge gained from this study may in the future help others with primary immunodeficiencies.

Alternative Approaches or Treatments

There are options you may consider other than participating on this trial, including:

- Continuing to receive medications for your current infections, cancers, autoimmune problems, or other complications as they arise.
- You may also be eligible to receive transplant for your disease outside of a research study at another transplant center.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by your disease. It does not treat the disease directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.
- Another option is not to receive any further treatment at all.

You should discuss with your referring doctor and your doctors at the NCI whether or not any of these other treatments might be a reasonable choice for your disease.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if you become pregnant
- if your disease comes back during treatment

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- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases **cannot** be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigators involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.



Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

COMPENSATION, REIMBURSEMENT, AND PAYMENT**Will you receive compensation for participation in the study?**

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY**Will your medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance

that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.



RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dimana Dimitrova, M.D. by phone at 240-858-3647 or email: dimana.dimitrova@nih.gov. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant

Print Name of Research Participant

Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR

Print Name of LAR

Date

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian

Print Name of Parent/Guardian

Date

Signature of Parent/Guardian (*as applicable*)

Print Name of Parent/Guardian

Date

Assent: I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Minor:

Signature of Minor

Print Name of Minor

Date

Investigator:

Signature of Investigator

Print Name of Investigator

Date

Witness should sign below if either:

1. A short form consent process has been used to enroll a non-English speaking subject or
2. An oral presentation of the full consent has been used to enroll a blind or illiterate subject

Signature of Witness_____
Print Name of Witness_____
Date**NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

_____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

_____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.

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