INSTITUTE: National Cancer Institute

STUDY NUMBER: 04-C-0095 PRINCIPAL INVESTIGATOR: Steven Pavletic, M.D.

STUDY TITLE: A Pilot Study of Intensified Lymphodepletion Followed by Autologous Hematopoietic Stem Cell Transplantation in Patients with Severe Systemic Lupus Erythematosus

Latest IRB Review: Continuing Review 10/31/05
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Description of Research Study

We invite you/your child to participate in a research study of autologous stem cell transplantation to treat severe systemic lupus erythematosus (also called SLE or simply "lupus") because you/your child have lupus affecting a major organ and did not respond to standard treatment. SLE is a chronic, inflammatory, disorder of the immune system that may affect many organs. It is called an autoimmune disease because your/your child's body has developed an immune reaction against itself.

The main purpose of this study is to determine whether we can achieve long-term remission of your/your child's lupus by using high doses of drugs to completely shut off your/your child's immune system and then giving you/your child back your/your child's own blood stem cells that can rebuild a "new" more normal immune system. We hope that this

treatment will make your/your child's lupus stay in remission for years without further treatment. We plan to enroll a total of 14 patients in this study at the NIH.

Another important aim of this study is to learn more about your/your child's disease by studying your/your child's blood, bone marrow cells, lymph node tissue, and other tissue that are affected by lupus. Blood samples that we collect after transplantation, when the immune system and the disease are suppressed, give us a unique opportunity to study lupus. These samples may be useful in developing more efficient treatments for lupus. We also would like to evaluate the quality of your/your child's everyday life through a series of questionnaires that we will ask you/your child to complete during this study.

The drugs and treatments that we use in this study have all been approved by the US Food and Drug Administration, (FDA), for use in other diseases. You/your child may have received some of the drugs during previous treatment of your/your child's lupus. What is experimental about this study is that we are using these drugs in a new combination at different doses and in combination with transplantation of your/your child's own blood stem cells. The combination of drugs rituximab, fludarabine, and cyclophosphamide is considered investigational for the treatment of lupus.

In this study we are collaborating with several other institutes at NIH. The primary investigators are physicians at the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and of the National Cancer Institute (NCI) transplant team. Investigators at these institutes are very experienced in treating patients with lupus and in the transplant procedure. The following information may be helpful in helping you/your child decide whether you/your child want to participate in this study.

Background

Lupus is an autoimmune disease, caused by an abnormal immune reaction against your/your child's own body. Certain cells within your/your child's blood, called lymphocytes play an important role in this reaction. Under normal conditions, lymphocytes protect your/your child's body from infections by directly attacking invading organisms or by producing antibodies against them. However, in autoimmune diseases, such as lupus, lymphocytes are out of control and they turn against your/your child's own body and produce antibodies that may damage your/your child's own organs. These are called autoantibodies. In patients such as yourself or your child, whose major organs are attacked, lupus can be life threatening. Patients like yourself or your child who have severe lupus often require long term treatment that suppresses the immune system. Although these treatments may control lupus they are associated with serious side effects such as increased risk of severe infection or early heart disease. The most effective treatments all target some types of lymphocytes, but in most cases they do not remove all harmful lymphocytes and autoantibodies. The goal of this innovative treatment is to remove as much of your/your child's immune system as possible and replace it with your/your child's own stem cells.

All lymphocytes originate from the mother cell in the bone marrow called the "blood stem cell". These cells keep multiplying in the bone marrow during our lifetime and can develop into any form of mature blood cell. Examples of these blood cells include the red blood cell (carries oxygen to our organs), the white blood cells, such as neutrophils and lymphocytes (help to fight infection), and blood platelets (prevent us from bleeding). Collecting these blood stem cells and giving them back to the patient through a vein is called a "transplant". The process of giving them back usually occurs

after high doses of drugs are given to remove the "old" immune system. The use of a patient's own blood stem cells for this procedure is called an "autologous blood stem cell transplant".

Blood stem cell transplantation has been used increasingly worldwide since 1968 to treat leukemia (a form of bone marrow cancer) and aplastic anemia (an autoimmune disease that attacks and destroys the bone marrow). Currently, about 15,000 patients receive some form of blood stem cell transplantation each year in North America for a variety of cancerous or non-cancerous diseases. Since 1996 about 500 patients with different autoimmune diseases, including nearly 100 with lupus, have been treated worldwide with autologous stem cell transplantation.

Most autologous transplantation studies in lupus have involved people who were in very advanced stages of the disease and who were frequently very sick. Major responses (disappearance of lupus) were achieved in about 65 percent of patients and three-quarters of these responses lasted over 2-3 years. The risk of getting a serious infection when the immune system is not working is an ever-present concern. Such infections can occur after people receive high doses of drugs to eliminate all cells in the immune system and before the new stem cells given during transplant become active. In these early transplant procedures some transplant-related deaths did occur. In this study we will combine drugs in a new way to hopefully further improve disease response and the safety of the autologous transplant procedure in lupus. The clinical team conducting this study consists of physicians and nurses that are national leaders and highly specialized and experienced in treating lupus and in performing stem cell transplantation procedures for autoimmune and other diseases.

Overview of the Research Treatment Plan

If you/your child participate in this study you/your child will undergo the following procedures and tests listed in the order in which they will occur. Further details will be included in later sections:

- **Screening**: You/your child will undergo two screenings. First, a rheumatologist will determine whether your/your child's lupus meets the treatment criteria. Second, the NCI transplant team will determine whether you/your child is physically strong enough to tolerate the transplant procedure.
- **Central Venous Catheter Insertion**: You/your child will have a small plastic tube placed through a vein in your/your child's upper chest wall or neck for blood drawing purposes as well as for administering medications. This insertion may be scheduled before apheresis or before priming. Further information is provided on Page 5 of this consent. The catheter will be used for the duration of your/your child's transplant procedure and immediate follow-up treatment.
- **Apheresis:** You/your child will undergo a one to two hour procedure performed in the Blood Bank where technicians will collect some of your/your child's white blood cells solely for research purposes (described below). This research blood work will be repeated about 7 times during your/your child's participation in this study for research purposes only. Apheresis procedure will also be the procedure used to collect your/your child's stem cells for transplant. That cell collection will require a 3 to 5 hour procedure daily for 1 to 3 days in a row.
- **Priming**: Three medications will be administered through a tube in your/your child's vein followed by a daily injection of one medication under the skin. We will use these medications to increase the number of blood stem cells for collection and to help control your/your child's disease. We will then collect the stem cell through a process called apheresis.

- **Conditioning:** Medication will be given through a tube in your/your child's vein to eliminate all white blood cells from your/your child's blood and bone marrow. You/your child will be admitted to the hospital for this procedure which will be done about 1 to 2 weeks after stem cell collection.
- **Transplant:** The stem cells collected from your/your child's blood will be given back to you/your child through a tube in your/your child's vein. It will take several days for the new cells to begin to circulate throughout your/your child's blood stream. You/your child will be closely watched in the hospital until you/your child fully recover your/your child's bone marrow. The day of the infusion will be called "Day 0" because it is the starting point for all your/your child's future exams and follow-up visits. You/your child will be discharged from the hospital about two weeks after you/your child receive the stem cell infusion.
- **Steroid Taper:** We will continue daily prednisone doses throughout the conditioning treatment. We will then lower the doses gradually with a goal of stopping the prednisone permanently. This will occur over 12 months. During that time we will closely monitor you/your child for any signs that your/your child's disease is coming back. If there is evidence that your/your child's lupus is coming back, your/your child's participation in this study will stop and you/your child will receive a standard treatment approach for your/your child's lupus.
- **Follow Up:** The most frequent follow-up visits will take place during the 2 to 3 months after your/your child's transplant. Follow-up visits will take place at the NIH Clinical Center. We will continue to follow your/your child's progress every 3 to 6 months during the first two years and then at less frequent intervals for up to five years.
- Questionnaires: During regular post-transplant follow-up visits we will give you/your child several questionnaires to assess the activity and the effects of treatments on the quality of your/your child's everyday life. Completing these questionnaires will take about 30-45 minutes.

Screening:

Disease (Lupus) Evaluation

On your/your child's first screening visit you/your child will have a complete medical history and physical examination in the NIAMS lupus clinic. You/your child will meet with members of the rheumatology lupus team who will review your/your child's medical history and determine whether transplantation would be a reasonable treatment option for you/your child.

You/your child will have several blood, urine, and radiology tests to evaluate the extent of your/your child's disease. These tests are performed routinely during lupus evaluation. We will obtain about 10 tablespoons of your/your child's blood to evaluate your/your child's bone marrow, kidney, liver, thyroid and immune system function. A blood sample will also be sent to the NIH Blood Bank to determine your/your child's blood group and also to perform routine tests of past virus exposure. Viral testing will include hepatitis and human immunodeficiency virus (the virus that causes AIDS). The results of the viral tests may determine whether you/your child qualify for the transplantation procedure. You/your child will be asked to sign a separate consent form for the HIV testing. For women of child-bearing potential we will perform a blood pregnancy test. You/your child will not be eligible to participate in this study if you/your child are pregnant.

Depending on which of your/your child's major body organs have been affected by lupus, you/your child may be asked to undergo additional testing. These tests are also used routinely to evaluate lupus. These tests may include a lumbar puncture to examine the fluid around your/your child's brain and spinal cord, a kidney biopsy, and/or a lung biopsy. The NIH Laboratory of Pathology will review all samples from the biopsy procedures to confirm the presence of lupus. If your/your child's lung(s) are involved, you/your child will also be asked to undergo a procedure called bronchoalveolar lavage, to confirm the diagnosis.

A computerized tomography (CT) scan of your/your child's chest will also be done. Brain and spine MRI (magnetic resonance imaging) scans will be performed if central nervous system (CNS) disease is present. Neurocognitive tests (questionnaires) to measure your/your child's thinking function (memory, orientation and others) will also be given.

NCI Transplant Evaluation

The NCI transplant team will also perform a history and a physical examination focused on the medical elements that are important for the transplantation procedures. This will include a thorough review of all previous blood test results. Additional testing and evaluation will include reproductive endocrinology consultation, chest x-ray, social work consultation, heart imaging by ultrasound or by radioisotope (MUGA) scan to evaluate heart function, electrocardiogram (heart beat tracing) and pulmonary function tests (breathing test). Other specific serum or urine diagnostic studies may be performed as necessary to thoroughly evaluate your/your child's health status.

You/your child will also undergo a bone marrow aspirate and biopsy from one of your/your child's pelvic bones to evaluate the health of your/your child's blood and marrow cells. This test is performed by first numbing the iliac (hip) bone with a local anesthetic called lidocaine. We will make a small cut in your/your child's skin, insert a needle into your/your child's iliac bone, and remove about two tablespoons of liquid from your/your child's bone marrow through the needle. A small fragment of the bone marrow will also be removed with the needle.

Once we have confirmed your/your child's eligibility for this study and you/your child have decided to participate, your/your child's medical care will be transferred to the NCI transplant team. This care will continue until discharge from the NCI day hospital and outpatient service, about 2 to 3 months after the transplant. Your/your child's rheumatologist will continue to be closely involved in all of your/your child's care.

The following studies may be repeated or additionally completed at the NCI with the transplant team before you/your child start the priming regimen: a brief history and physical, 10 tablespoons of blood for evaluating blood counts and blood chemistries, lupus antibodies and complement, pneumococcal and tetanus serum titers, endocrine function studies, tissue typing (in case more intensive platelet transfusion support is needed).

Other evaluations will include: nutritional assessment consult, social work consult, dental consult, tuberculosis (TB) PPD skin testing for prior tuberculosis exposure, and urine analyses.

If you agree to proceed with these research studies, we will also do an ultrasound to find enlarged lymph nodes, perform fine needle aspirates for conventional cytology and research studies, and also perform a baseline PET scanning that will be described in detail later.

Additional tests will include quality of life questionnaires, disability functional testing (HAQ), and neurocognitive (thinking) assessments.

You/your child must avoid becoming pregnant during your/your child's participation in this study because of possible risk to the mother and baby's health. If you/your child are a male, you/your child should not make somebody pregnant for at least the first six months after the transplant. You/your child must be willing to practice effective birth control during treatment and for the 2-year period after the transplant (if you/your child are a female), or for at least 6 months after the transplant (if you/your child are a male).

If you are an adult you will be encouraged to name someone as your "durable power of attorney". This person should be someone who you trust to make medical decisions for you if you become physically or mentally unable to make your own treatment decisions.

Your/your child's participation in this study may be restricted depending upon the previous treatments you/your child may have had. Your/your child's participation in this study may also keep you/your child from being in other research studies while you/your child are enrolled in this one.

Central Venous Catheter

We will insert a central venous catheter into a vein (thin plastic tube placed through a vein in the upper chest or neck and advanced into a large vein near the heart). This procedure will be scheduled before you/your child receive any transplant related treatment. The catheter will be used throughout your/your child's transplant procedure and follow-up treatment. This type of catheter is sometimes called a "Hickman catheter". We will use it to collect your/your child's stem cells during apheresis procedures, and to administer your/your child's priming and conditioning medications, fluids, transfusions, and other medications such as antibiotics. We can also use it to draw blood samples for tests. We will need blood samples often during your/your child's treatment (about 4 to 10 teaspoons of blood, at least once daily during your/your child's hospitalization for transplantation and about 4-10 teaspoons per week at other times) and the catheter will make drawing blood easier and less painful. We will use most of the blood to monitor your/your child's health during and after your/your child's treatment. We will draw research blood samples and routine blood samples at about the same time.

There is a chance that the catheter could become infected or a blood clot may form within the catheter. If this happens, we will remove it and replace it with a new one. To prevent clotting, we will need to flush the catheter regularly. This catheter will be removed as soon as you/your child do not need intravenous treatments or frequent blood draws.

Treatment Plan:

Priming Regimen

The purpose of the priming regimen is to: 1) provide enough stem cells for collection for transplant, 2) provide temporary control of your/your child's lupus, 3) provide initial removal of lymphocytes from your/your child's body and from the stem cells to be collected, and 4) prevent some drug side effects during the conditioning regimen. Before priming you/your child will need to stop all medications you/your child are currently taking to treat your/your child's lupus, except corticosteroids.

We will provide most of the priming treatment in the outpatient clinic but a brief hospital admission before apheresis may be necessary. We will give all medications intravenously (through the vein) through the central venous catheter. This procedure is normally referred to as chemotherapy (treatment of a disease by drugs).

Day 1- Methylprednisolone will be given as a one time high dose given over 30 minutes.
Rituximab will be started slowly and adjusted to be given over 1-2 hours. You/your child will receive Tylenol and Benadryl by mouth 30 minutes before the medication starts to reduce the chance of an allergic reaction.

Day 2- Intravenous fluids will be started early in the morning to keep you/your child well hydrated and to encourage frequent urination.

Cyclophosphamide will be given over 2 hours. Intravenous fluids will continue about 7 hours after this treatment.
Mesna will be given immediately prior to cyclophosphamide and repeated at 4 and 7 hours after the first dose. This drug helps protect the bladder from injury by cyclophosphamide (explained further under "Risks or Discomforts of Participation").

Day 4- Rituximab dose will be repeated over 1-2 hours.

Day 6- G-CSF (growth factor) will be started by a small injection under the surface of the skin. This drug will help increase the number of blood stem cells your/your child's body produces. These injections will be given once a day until the number of stem cells in the blood is high enough for stem cell collection (apheresis) which usually occurs about 10 days after the cyclophosphamide has been given.

Blood Stem Cell Collection by Apheresis.

Apheresis is done in the Department of Transfusion Medicine (Blood Bank) and is supervised by Blood Bank doctors. About ten days after starting the priming regimen, your/your child's blood stem cells will be collected by apheresis. This procedure takes three (3) to five (5) hours to complete, during which you/your child will remain in a bed or a reclining chair. During the procedure, the newly formed blood stem cells that after administration of G-CSF have moved from you /your child's bone marrow into the blood stream will be collected. We will draw your/your child's blood into an apheresis (cell separator) machine, which will separate the white blood cells from the red blood cells and plasma through a spinning process. The white blood cells will be collected into a bag, and the red blood cells and plasma will be returned to you/your child. In most cases, the intravenous catheter we inserted to receive your/your child's treatment drugs will also be used for the apheresis procedure. However, we may need to place one or two additional intravenous lines in your/your child's arm, or to have a single, larger intravenous line placed in a vein in your/your child's groin until the apheresis procedure is finished.

Stem cell collections by apheresis will be performed daily for one to three days in a row until enough stem cells are collected. The collected cells will be processed in a special device in the Blood Bank to separate out the stem cells. As far as possible, all other cells will be removed, especially lymphocytes, to avoid giving them back to you/your child. This process is called "CD34 cell selection". The separated stem cells will be frozen and then thawed for infusion at the time of transplant. These cells will help your/your child's bone marrow and blood counts recover much faster after the high-dose therapy.

We will store the other cells that were removed and that contain mostly lymphocytes for the very rare possibility of an infection that would require their infusion to boost the recovery of your/your child's immune system. We will obtain a small sample of your/your child's collected cells, stem and non-stem, for the purpose of quality control and research purposes. We can not give you/your child the results of the research blood draws because we can not interpret them accurately enough for clinical patient care. If we develop meaningful information that may be important to your/your child's health, we will inform you/your child of these results.

You/your child should understand that there is a small possibility we may not be able to collect enough stem cells. Also, there is a very small possibility that your/your child's stem cells could be damaged or lost in the process of separating or freezing them. In any of those unlikely situations, you/your child would not be able to proceed with the transplant part of this study. You/your child would be removed from the study at this point and would not complete the remaining treatment.

Research (Apheresis) Blood Samples: We may perform apheresis to collect a large number of white blood cells for research purposes. This apheresis procedure will require about 1-2 hours. We may also repeat this procedure at one month follow-up and every 3 months after transplant for the first year and every 6 months during the second year. It may also be repeated if at any time your/your child's lupus starts showing signs of coming back. The collected white blood cells will be analyzed in research laboratories and may be stored frozen for future lupus research. We will not give you/your child the results of the research blood draws because we can not interpret such results accurately enough for clinical care. If we develop meaningful information from this study that may be important to your/your child's health, we will inform you/your child of any useful results when they become available.

Conditioning/Transplant (Infusion of your/your child's blood stem cells)

If we have collected enough of your/your child's stem cells and no other events occur that would prevent you/your child from having transplantation, you/your child will be admitted about eight days before transplantation to the Experimental Transplantation Unit of the NCI's Medical Oncology Clinical Research Unit at the NIH Clinical Center.

Conditioning:

The day of transplantation (infusion of your/your child's stem cells) is called "Day 0". All medications will be given through your/your child's central venous catheter unless otherwise listed below. The conditioning regimen works to eliminate most of your/your child's lymphocytes (white blood cells) that are thought to be responsible for worsening your/your child's disease. The conditioning treatment will begin 7 days before the day of transplant and will be referred to as "minus days" until the day of transplant as follows:

Day –7 Rituximab will be given in one dose (two times the amount you/your child received before)
Day –6 Fludarabine will be given over 30 minutes. This will be repeated once a day for 4 days
Cyclophosphamide will be given over 2 hours. This dose will be 2 and ½ times the amount you/your child received before. This dose will be repeated once a day for 4 days.
Intravenous fluids will also be given continuously for 4 days.
Mesna will be given continuously for 4 days starting concurrently with the start of cyclophosphamide. This drug helps protect the bladder from injury by cyclophosphamide (explained further under "Risks or Discomforts of Participation").

Day –5 Fludarabine, Cyclophosphamide, Mesna
Day –4 Fludarabine, Cyclophosphamide, Mesna
Day –3 Fludarabine, Cyclophosphamide, Mesna
Day –2 Rest
Day –1 Rest
Day 0 Transplant-You/your child will receive your/your child's stem cells (Day Zero).
Your/your child's stem cells will be thawed and infused through your/your child's central venous catheter. These stem cells are given in a small amount of a highly concentrated stem cell product. Reactions to this infusion are very rare.
Days will then be referred to as "plus" days after Day 0.
Day +1 G-CSF injections will again be started once per day. This will continue until your/your child's blood counts begin to recover usually around day +8.

Monitoring: You/your child will be watched very closely after transplantation for possible complications (especially infections), which are described below. In the hospital you/your child will be seen daily by a team of physicians, nurses, and nurse practitioners and you/your child will receive standard supportive care, such as antibiotics, growth factors (G-CSF), red blood cell and/or platelet transfusions, and (needed rarely) intravenous nutrition to prevent or treat these problems, until your/your child's blood counts recover.

We will draw blood daily during your/your child's in hospital treatment and also frequently thereafter during the immediate post-transplant outpatient follow-up period. We will use most of the blood draws to monitor your/your child's health during and after the chemotherapy and transplant procedure. In addition, we will draw some blood samples for research purposes. We will use these samples to study how your/your child's immune system and disease are affected by the transplant chemotherapy and the stem cell transplant itself. The total amount of blood that will be collected during any 6 week period will not exceed 450 ml, the amount you would give during a single blood donation.

Once your/your child's stem cells have engrafted (neutrophil cells increase in number to over 500 for at least three days in a row) and you/your child feel strong enough (usually 2-3 weeks after transplantation), you/your child will be discharged from the hospital and followed closely as an outpatient in the NCI transplant clinic and the day hospital.

Steroid Taper/Follow-Up

You/your child will begin decreasing the daily doses of corticosteroids after discharge from the hospital. During this early recovery period, you/your child will be required to remain in the Washington, D.C. area for about two months after transplantation to be monitored for complications as well as disease symptoms. You/your child might need to be re-admitted to the hospital for complications related to infections or lupus.

You/your child must not use any over the counter drugs or receive any vaccines without consulting with the investigator first.

Long-term Follow-up After Transplant

After 3 months, you/your child will have follow-up visits in the NIAMS and NCI clinics at least every three months during the first year and every six months during the second year after transplant. You/your child will then be followed at least yearly for five years. If you/your child are in good health after the two to three-month post-transplant period, you/your child will be allowed to return home to the care of your/your child's primary physician.

During the return visits you/your child will be scheduled to have physical exams, blood draws, urine sample tests, bone marrow aspirates and biopsies, lumbar punctures (if CNS lupus) and other appropriate biopsies and tests to further monitor your/your child's disease status. Bone marrow biopsies and ultrasound-guided fine-needle aspirates of lymph nodes will be scheduled at 6, 12, and 24 months post-transplant or at time of documented lupus flare or progression.

An additional bone marrow biopsy would be offered solely for the research purposes at day -1 prior to stem cell infusion. Since this particular bone marrow sampling would be solely for research purposes you may opt out of the routine bone marrow biopsy at day -1 (see and sign below)

If you are a person 18 years of age or older please circle below and initial if you agree or disagree to undergo bone marrow biopsy solely for research purposes on day -1 (day before stem cell infusion). This research procedure is not offered to patients younger than age 18:

Agree: Disagree:

Initials: Initials:

Follow-up research PET scans will be scheduled at 1, 6, 12, and 24 months or at the time of documented lupus flare or progression.

During the regular clinic follow-up visits you/your child will also have additional blood draws and short apheresis procedures to obtain blood for research purposes to study how your/your child's immune system recovers after the transplant.

Questionnaires: At the time of regular follow-up visits after your/your child's transplant you/your child will be also be given various questionnaires to assess your/your child's disease status and the effects of transplantation treatments on the quality of your/your child's everyday life.

Antibiotics: You/your child are also likely to receive some oral (taken by mouth) antibiotics to prevent infections for about a year after transplant. Because your/your child's "old" immune system was in large part eliminated with the transplant procedure, at the one year follow-up visit you/your child will also be started on a vaccination schedule using non-live vaccines against common agents. These shots will be given at 12, 18 and 24 months after transplant.

Duration of Study: You/your child will be a part of this study for five years. The most frequent follow-up will be during the first two years after transplantation.

PET scan (Research Purposes Only)

We will perform a PET scan to further evaluate disease activity within your/your child's lymph nodes. Lymph nodes are located not only in places that we can touch, like our neck or armpits, but also are found deep inside our chest and abdomen. Without PET scans it would be impossible for us to obtain information on lymph node activity without surgery, and PET scanning may serve this purpose. Although PET is not a therapy for SLE, we are using it in this study to find out whether it is helpful to study white blood cell activity and the pattern involved within lymph nodes in lupus. Outside of a research setting, doctors would not routinely use the PET scan to evaluate lupus.

PET scanning uses a radioactive sugar molecule. This molecule is called fluorodeoxyglucose, or FDG for short, and is similar to glucose, the sugar that the body uses for fuel. The FDG is labeled with a type of radioactivity called Fluorine-18 (F-18) which can be detected and viewed on the computer screen with our special PET camera. Although doctors use the FDG routinely for clinical imaging of disorders such as cancer, heart disease and epilepsy, in this study the FDG will be

used as an FDA approved investigational new drug for research use. We believe that activated lymphocytes use more FDG because these cells burn more glucose fuel.

In previous studies we have found that patients with lupus have FDG activity present in their lymph nodes that is not seen in healthy people. We will perform a baseline study and after the transplant we will repeat the PET scan about five times to help evaluate the presence of lupus activity.

You/your child will be seen in the Nuclear Medicine Department where an FDG-PET scan will be performed. Although you/your child will not be permitted to eat anything for 6 hours before the test, you/your child may drink as much water as you/your child wish. If possible, you/your child should drink 2 to 3 glasses of water before the test. A small plastic catheter ("IV") will be inserted into a vein in one arm for injection of the FDG. You/your child will receive the FDG intravenously and will rest quietly in a room for 1 hour after which the PET scan will be performed. The PET camera is shaped like a doughnut, circular with a central hole. You/your child will be asked to lie flat on your/your child's back on a soft cradle that will be inserted into the central hole of the camera. Over the next 2 hours after the FDG injection the picture-taking process will take place. A technologist will be present at all times and a physician will be available. If for any reason you/your child feel that you/your child cannot continue, the scanning can be stopped and you/your child can be removed from the scanner immediately. However, the information from the scan may be lost at that time. You/your child will lie on your/your child's back on a scanning bed and several scans will be made of your/your child's body. This will require that you/your child lie quietly and without moving your/your child's head or arms. After the scan is finished, you/your child will be asked to empty your/your child's bladder at regular intervals of approximately 1½ hours for 6 hours to remove the radioactive sugar in the urine.

Removal from Study: It is important to know that you/your child may be removed earlier from the study in the following situations: collection of insufficient stem cell dose, serious toxic effects during priming, major lupus progression, and/or if the principal investigator feels that your/your child's continuation on the study would create an unacceptable risk to you/your child. You/your child are also free to withdraw at your/your child's own request at any time.

Alternative Treatment

Several drugs are effective in treating lupus. To be eligible for this study you/your child must have already received and not responded to some or all of these drugs. Most of these drugs suppress your/your child's immune system to decrease the amount of damage lupus does to your/your child's body. These are your/your child's options:

- Standard immunosuppressive therapy with drugs, such as prednisone, cyclophosphamide (Cytoxan), mycophenolate mofetil (Cellcept), azathioprine (Imuran) and chlorambucil (Leukeran), methotrexate and cyclosporine (Neoral). Although these drugs effectively treat lupus, they have some possibly serious side effects and may not work in all patients. Most of these drugs have to be given for prolonged periods of time and lupus recurs commonly after they are stopped. We do require that you/your child have received and not responded to treatments that we usually use for patients like you/your child. The exact details of these treatments are described in the protocol and are based on the organs involved. However, we do not require that you/your child have failed all possible therapies. For example, for patients with kidney disease we require that they fail six

months of cyclophosphamide but we do not require them to fail mycophenolate mofetil (Cellcept) as well, which in the opinion of some lupus experts, has similar efficacy and should be tried first in patients who do not respond to cyclophosphamide. The reason we do not require this is that if you/your child do not respond to any of these therapies the disease may lead to permanent damage that would not be improved by stem cell transplantation.

- Various experimental protocols at other institutions. These include autologous stem cell transplantation using a different conditioning regimen and treatment with high-dose cyclophosphamide without stem cell transplantation.

Therefore, before you/your child decide to enter this study, you/your child must discuss the advantages and disadvantages of each treatment with your/your child's physician.

Risks or Discomforts of Participation

Your/your child's doctors will try to limit the toxicities and side effects you/your child experience using all means, but treatment with high-dose chemotherapy can result in permanent disability or death. We do not know the effects these medications (treatments) may have on an unborn child. For this reason, you/your child are not eligible for this study if you/your child are pregnant and you/your child will be asked to practice an effective method of birth control while you/your child are participating in this study.

General: The side effects of high doses of chemotherapy are likely to result in a need for antibiotic therapy to fight infection and for transfusion of blood products, including red blood cells (to treat anemia) and platelets (to prevent bleeding). In addition, you/your child may need other medications for comfort or to treat other medical conditions. Antibiotics carry the risk of allergic reactions with each antibiotic having its own risks and side effects. The transfusion of blood products carries the risk of viral diseases, although this risk is low, as all blood products given at the Clinical Center are tested for HIV and known Hepatitis viruses. The transfusion of red blood cells can cause fever, itching, chills, rash, low blood pressure, shortness of breath and rarely, more serious reactions, such as the immune destruction of red blood cells (hemolytic anemia). The infusion of platelets can cause similar side effects. The thorough testing and matching of blood products makes these side effects less likely, but mild reactions to transfusions are not uncommon. Fludarabine may increase your risk for a rare but potentially lethal complication of blood transfusion, called transfusion associated graft versus host disease. Fortunately, there is a way to prevent this from happening by using irradiated blood products (platelets or red-blood cells) for transfusion. You will receive only irradiated blood products at the NIH but it is very important that you let your physician and family members know that you should only receive irradiated blood products should you require platelet or red-blood cell transfusions for at least 1 year after the end of this protocol. We will also provide you with a medical alert bracelet and a card indicating this.

Each of the chemotherapy drugs and other drugs underlined below has the possible side effects listed. We do not expect that patients will experience all of these side effects. However, the experimental nature of this study - combining these agents in a new way - may lead to new or unexpected side effects.

1) Failure of blood counts to return after stem cell re-infusion resulting in prolonged (occasionally permanent) life threatening anemia, bleeding and/or infection (risk is estimated at about 1%)

Death due to the complications of this transplant procedure in lupus are not known but based on prior experiences with similar regimens in other diseases and with other regimens in lupus, this number is estimated to be up to 5% (1 in 20). Due to the absence of larger published studies of transplants in SLE it is difficult to quote mortality rates of transplanted patients from the literature but risks of transplant-related deaths in protocols for lupus patients could vary from 3% to up to 12%.

Bone Marrow Aspiration and Biopsy: This procedure usually causes only mild pain for a short time at the biopsy site during the procedure. Very rarely, bleeding, prolonged mild pain, or an infection may occur at the biopsy site.

Kidney Biopsy: This will be performed before transplantation, at one year after transplantation and at any time when medically necessary, only if you/your child have lupus in your/your child's kidneys. During this procedure, two specimens are obtained from your/your child's kidney using a specially designed needle. We ask your/your child's permission to obtain a third specimen for research purposes. To do this we have to make a third pass of the biopsy needle. Renal biopsy is a procedure that is associated with several possible complications. To reduce the risks of kidney biopsy, we will perform the biopsy after your/your child's kidney has been located with the help of a CT-scan (a special, computerized form of X-ray). The nephrologist performing the biopsy will discuss the potential complications in more detail before the procedure. The risks associated with the procedure will be increased as a result of obtaining the additional biopsy specimen. These risks include the risk for bleeding and infection. Clinically significant bleeding requiring blood transfusions occur in 0.1% to 3.8% of patients. Surgery for persistent or massive bleeding is required in less than 0.2% of patients. Infections are unusual except in the presence of active infection of the kidneys. Other complications, including loss of the biopsied kidney and laceration of the liver, spleen, or other internal organs are extremely rare. If a surgical procedure is required to correct any of these problems there is a small risk of death, which is related to the general health of the patient. If during the course of the procedure any problems are encountered that suggest an increased risk for the third pass of the biopsy needle, the third pass will not be performed.

While kidney biopsies before transplant and in the case of disease recurrence are medically indicated for the evaluation of your lupus, routine kidney biopsy ay 12 months post-transplant in the absence of other reasons would be done solely for research purposes and you may opt out from doing this at that time-point (see and sign below).

If you are 18 years of age or older please circle below and initial if you agree or disagree to undergo routine kidney biopsy at 12 months post transplant solely for research purposes. This research procedure is not offered to patients younger than age 18:

Agree:	Disagree:
Initials:	Initials:

Bronchoscopy and Bronchoalveolar Lavage: We will perform this procedure before transplantation and at one year after transplantation and additionally when medically necessary, if you/your child have lupus in your/your child's lungs. We will pass a long, narrow, flexible tube (bronchoscope) through your/your child's nose or mouth into the airways of your/your child's lung. Before we pass the tube, we will spray your/your child's nose and throat with local anesthetic (numbing medicine). The intravenous catheter will be placed to allow for the administration of agents which will produce mild sedation. These agents are a valium type drug called versed and a morphine type drug called fentanyl. The procedure will be performed by senior physician staff in the Clinical Center with experience in performing bronchoscopy and related procedures. The procedure will take about 30 minutes.

When we have steered the bronchoscope into a specific airway of the lung, a small amount of sterile water may be squirted through it into the lung and immediately suctioned back to wash off some of the cells lining the airways. We will then analyze the fluid and cells in the laboratory. Some discomforts and risks are associated with this procedure. There is no known risk of this procedure in individuals with normal hearts and lungs, but as a precaution we will monitor heart rhythm and rate. Drugs that produce sedation may be associated with the development of a lowered blood pressure or with decreased rate of breathing. We will monitor your/your child's blood pressure, respiratory rate and oxygenation during the procedure. You/your child may feel some discomfort when we pass the bronchoscope through the nose, and a few patients experience gagging and an urge to cough when the bronchoscope passes through the throat and the vocal cords. A sore throat and mild hoarseness may persist for several hours; these resolve routinely within a day. Occasionally, subjects have a temporary fever following bronchoscopy; in hundreds of studies carried out to date by our pulmonologists, such fevers have gone away promptly and have required no therapy other than an aspirin-like medication.

While bronchoscopy and bronchoalveolar lavage before transplant and in the case of new clinical symptoms post-transplant are medically indicated, routine procedures at 12 months post-transplant in the absence of other reasons would be done solely for research purposes and you may opt out from doing this at that time-point (see and sign below).

<u>If you are 18 years of age or older please circle below and initial if you agree or disagree to undergo routine bronchoscopy and bronchoalveolar lavage at 12 months post transplant solely for the research purposes. This research procedure is not offered to patients younger than age 18:</u>

Agree:	Disagree:
Initials:	Initials:

Lung Biopsy: We will perform this procedure before transplant if you/your child have lupus in the lungs and if this test is medically safe. This procedure allows for your/your child's doctors to examine small 1millimeter sized pieces of lung to look for evidence of lupus in the lung. These biopsies would be performed at the time of the bronchoscopy. There are two complications of the lung biopsies themselves. First, about 3% of persons will have some bleeding during the performance of the biopsies. Second, about 3% of persons will have air leak from the lung to the space between the lung and the chest wall causing the lung to collapse down. In about half of these cases, this problem is treated by the insertion of a tube through the skin and into the space between the lung and chest wall to draw out the air and re-expand the lung. A separate consent will be obtained for this procedure. It will not be repeated after transplant unless needed for regular medical care.

MRI: Magnetic resonance imaging (MRI) will be performed before the transplant and at least 7 times for post-transplant evaluations if you/your child have lupus in the brain or spinal cord. We also may use it as part of routine medical care, if medically necessary. MRI uses a strong magnetic field and radio waves to demonstrate structural and chemical changes in tissue. This technique is more sensitive than x-ray in some diseases and carries no radiation risk. You/your child will lie on a table in a space enclosed by a metal cylinder (the scanner itself). You/your child will need to stay within the cylinder for 1-2 hours. You/your child will be asked to lie very still for 10 to 15 minutes at a time. Some discomforts and risks are associated with this procedure: Patients are at risk for injury from MRI if they have metal objects in their bodies, such as pacemakers, aneurysm clips (metal clips on the wall of a large artery), metallic

prostheses, cochlear implants, or shrapnel fragments. Welders and metal workers are also at risk for eye injury because of unsuspected tiny metal fragments there. Individuals with fear of confined spaces may become anxious during MRI. You/your child will hear a thumping noise created by the radio waves forming the images. You/your child will feel no pain, but you/your child may find the noise and the closed-in space discomforting. The MRI operators will observe you/your child at all times, and you/your child will be able to speak to them; you/your child can ask to be moved out of the machine at any time.

Lumbar Puncture: The lumbar puncture (LP) or spinal tap allows us to study cerebrospinal fluid (CSF) to learn some of what is going on in the brain and spinal cord, which are bathed by CSF. This procedure will be performed before transplant and at least 7 times for post-transplant follow-up, in case you/your child have lupus in the brain or spinal cord. It may be also performed in routine medical care if necessary. For LP you/your child will lie on your/your child's side, and we will numb an area in your/your child's lower back with the local anesthetic. Then we will collect about 2 tablespoons of spinal fluid. Some discomforts and risks are associated with this procedure: Some patients may develop a headache or backache following an LP. Prolonged headaches develop in only 1 in 50 to 1 in 200 people and usually subside within 1 week. The likelihood of having a headache may be diminished by lying flat in bed for 24 hours after the LP. In rare cases, post-LP headaches persist for months or years. Such headaches may result from continued CSF leakage at the LP site. If the headache lasts longer than 1 week, a "blood patch" can be done. A small amount of blood from your/your child's arm vein is injected into the area of the supposed leak to try to seal it. The blood patch relieves the headache in most (95 percent in some studies) patients.

Central Venous Catheter: The side effects of placing a central venous line in your/your child's chest wall include bleeding, bruising, blood clot, or pain in the area of insertion. Experienced physicians will place this line. They will discuss the above risks at the time of the line insertion. Rarely, placement of a central venous catheter can result in a collapsed lung. If a collapsed lung occurs, it may require hospitalization and temporary insertion of a plastic tube in your/your child's chest to re-expand the lung.

Blood Drawing: You/your child may experience mild pain or bruising at the site on your/your child's arm. There is a small possibility of fainting and infection. Similarly, there is a small risk of bleeding, blockage, or inflammation (infection) of the vessel. Discomfort generally does not last long and permanent damage is extremely rare.

Priming and Conditioning Regimen: You/your child need to be aware that this type of therapy is likely to reduce your/your child's white blood cells for several days and also weaken your/your child's immune system. This condition will place you/your child at increased risk of infection. Such infections can sometimes be very serious and may result in death. For this reason, if you/your child develop a fever higher than 101° F, you/your child must see your/your child's doctor immediately. If necessary, you/your child will be treated with antibiotics. Also, this chemotherapy will likely cause your/your child's platelet count to fall, which may place you/your child at increased risk of bleeding. If your/your child's platelet count becomes dangerously low, you/your child will receive platelet transfusions. Because the chemotherapy on this study involves a new combination of drugs, participants in this study may experience unexpected toxic effects.

Apheresis Procedure

You/your child may experience numbness or tingling around the lips or fingertips due to the blood thinner that is given during the procedure. This is easily treated by slowing down the procedure and giving calcium supplements. Blood infections from contamination of the apheresis machine are a remote possibility. On rare occasions, allergic reactions may occur during apheresis, or a participant may lose as much as a unit of blood due to machine malfunction. We treat

these events by stopping the procedure and giving antihistamines or intravenous salt solutions. We will make all attempts, including additional blood and platelet transfusions if needed, to protect you/your child from any complications of apheresis. This procedure takes three (3) to five (5) hours to complete, during which you/your child will remain in a bed or a reclining chair. You/your child do not need to be hospitalized for the procedure itself.

The following are known possible risks of each drug used:

Methylprednisolone and prednisone may cause stomach or bowel ulcers, elevated blood pressure, diabetes, increased risk of infection, weight gain, mood change, thinning of bones with increased risk of fracture, cataracts (eye lenses opacities) and rounding of the face.

Rituximab can cause serious and in rare cases fatal allergic reactions. Most reactions are associated with the first infusion and usually can be prevented or successfully treated with medications and slowing or stopping the infusion. Mild reactions are common during the infusion and may include fever, chills, itching, and skin rash. Other common reactions are mild shortness of breath, low blood pressure, elevated blood pressure, nausea, vomiting, throat swelling, headache, muscle aches, and dizziness. Rarely, in cancer patients, rituximab has caused kidney damage and serious chemical disturbances of the blood by killing a very large number of tumor cells quickly. This complication at times has required dialysis. Some cases have been fatal. Rarely a moderate and transient drop in white count can occur 2-5 months after administration of rituximab. Severe, sometimes fatal, skin reactions have also been reported. This is very rare.

Cyclophosphamide can result in nausea, vomiting, and (temporary) hair loss. It can result in fluid and electrolyte abnormalities. It can also cause bleeding in your/your child's bladder (hemorrhagic cystitis). You/your child will receive intravenous fluids and a drug called mesna to prevent bladder injury when you/your child receive the priming and the conditioning regimen. Damage to heart muscle can very rarely occur which can lead to heart failure.

Filgrastim (G-CSF) may cause bone and muscle pain, headache, fever and chills. Pain, bruising and swelling at the injection site can occur. In rare cases, an allergic reaction can occur with rash, itching, and difficulty breathing. Less common side effects include chest pain, and a decrease in blood pressure after the first injection; these reactions resolve once the drug has been stopped. Swelling and rupture of the spleen, requiring surgery and resulting in some deaths has occurred in very rare cases.

Fludarabine: The main side effects of fludarabine at these doses and when combined with cyclophosphamide are severe bone marrow and immune system suppression and decreased production of red blood cells, white blood cells, and platelets. Until your/your child's new stem cells start to produce adequate numbers of blood white cells, you/your child will be at significant risk for infections, bleeding and severe fatigue. These conditions will be treated with antibiotics and transfusions. Fludarabine can also cause nausea, vomiting, diarrhea, loss of appetite, swelling, skin rashes, internal bleeding, headache, fatigue, nervous system toxicity, and heart or lung injury. These side effects are uncommon at the doses we will use in this study. Fludarabine may predispose you to transfusion associated graft versus host disease, therefore it is important that you follow our recommendations on page 10 about using irradiated blood products only.

Mesna: This drug can cause nausea, vomiting, and diarrhea, fatigue, headache, limb pain and very rarely a drop in blood pressure.

Stem Cell Infusion: Because the donor cells are frozen in a drug called DMSO to protect them from the effects of freezing, patients receiving thawed stem cells sometimes will develop toxicity from the DMSO. This is usually mild and temporary. You/your child will be receiving concentrated selected stem cells in a very small DMSO volume, which is unlikely to cause any symptoms. If symptoms do occur, they may include fever and allergic reactions, such as skin rash, itching, difficulty breathing, and drop of blood pressure. If this occurs, you/your child will be treated with IV fluids and medications. DMSO may also cause a temporary "garlic-like" taste and odor. Since these will be your/your child's own blood stem cells (autologous), there is no known risk of transmission of HIV or any other diseases in receiving these cells.

Other Medications: You/your child will routinely receive several other drugs to prevent or treat various infections and other transplant-related complications. These medications and their common side effects are listed as follows:

Diphenhydramine (Benadryl) may cause tiredness, dizziness, upset stomach, disturbed coordination, dry mouth, flushing, or difficulty urinating.

Acetaminophen (Tylenol), has no known toxicities known with single doses given with infusions of rituximab.

Valacyclovir can cause nausea, vomiting, headache, dizziness, abdominal pain, bone pain, allergic reactions, mild liver inflammation, kidney injury, and abnormal nervous system function.

Fluconazole can cause nausea, vomiting, headache, skin rash, abdominal pain, and diarrhea. Rare but sometimes serious liver toxicity has also been reported. Fluconazole can increase the blood levels of other drugs, which can increase their effectiveness and/or their side effects.

Caspofungin (Cancidas) can cause fever, nausea, vomiting, flushing, infused-vein complications (e.g. phlebitis), and headache. Other possible symptoms include isolated reports of rash, facial swelling, pruritis (itching), sensation of warmth, or bronchospasm. Severe allergic reactions with blood pressure drop have been reported during administration of caspofungin. Elevations in liver tests are also possible.

Trimethoprim/sulfamethoxazole (Bactrim) may cause nausea, vomiting, loss of appetite, allergic skin rashes, and suppression of bone marrow function. Rare but severe reactions may affect the skin and bone marrow; these have sometimes been fatal.

Medroxyprogresterone acetate (Provera) for control of menstrual bleeding can cause nausea, breast tenderness, lactation, allergic skin reactions, increased acne and body hair growth, scalp hair loss, fluid retention, depression, jaundice, vaginal spotting, changes in cervical secretions, and blood clots.

Late Transplant Complications: There are a number of potential complications that could occur long after transplantation. These complications are not likely to happen with the conditioning regimen we will use in this study but they theoretically could affect any organ in the body including the heart, lungs, kidneys, liver, muscles, and brain. Receiving chemotherapy drugs, in particular cyclophosphamide alone or along with autologous SCT, places you/your child at a higher risk than normal people for developing a cancer later in life, particularly leukemia or pre-leukemic conditions. One purpose of the bone marrow exam before and after transplantation is to detect, as early as possible, any marrow damage that could theoretically occur. You/your child will be informed about any clinically important abnormalities detected by you/your child's non-research bone marrow studies.

Fertility-Sterility: This treatment may result in sterility (the inability to produce children) and this is why you/your child will be asked to see a fertility-sterility consultant to advise you/your child about the risks and treatment possibilities, all of which has to be taken under careful consideration by you/your child prior to making a final decision to participate in this study. It is also unknown what harmful effects this treatment may have on an unborn child and for this reason, you/your child will be asked to practice an effective method of birth control while you/your child are participating in this study (for 2 years if you/your child are a female and for 6 months if you/your child are a male).

Fine needle aspirate (FNA) of the lymph nodes (research purposes only): Ultrasound guided fine needle aspiration is considered a low risk procedure. Superficial location of the lymph nodes makes bleeding less likely since this can be easily controlled. We will use a thin needle (22 or 23 gauge), which is much smaller than needles used for other biopsy procedures, to remove cells from the detected lymph nodes by multiple quick up and down motions. Usually three needle insertions are required to get an adequate sample. The cells are then evaluated by a pathologist under microscope or used for research studies. Superficial FNA is performed on an outpatient basis under local anesthesia. We will measure the lymph node size for the later comparison. Possible risks include a slight burning pain at the needle-insertion site during local anesthesia and the remote possibilities of bleeding, localized infection or reaction to lidocaine and also, if the lymph node is in the lower neck or chest, a very small risk of an air leak in you/your child's chest (pneumothorax). The plan would be to perform such procedures before starting treatment, and at 6, 12 , and 24 months post-transplant. Since these procedures would be solely for research purposes you may opt out of doing them if you so desire (circle below and sign).

If you are 18 years or older please circle below and initial if you agree or disagree to undergo routine ultrasound guided fine needle aspirations of your lymph nodes solely for research purposes. This research procedure is not offered to patients younger than age 18:

Agree:	Disagree:
Initials:	Initials:

PET scanning (research purposes only): There are no known toxicities associated with the intravenous injection of small quantities of FDG.

Risks of radioactive exposure with PET: This research study involves exposure to radiation from FDG-PET scans and transmission scans. Please note that this **radiation exposure is not necessary for your/your child's medical care** and is for **research purposes only**. The total amount of radiation you/your child will receive from each PET scan in this study is from 15-millicurie (mCi) of FDG and the associated transmission scans. If you/your child are younger than 18 years old you/your child will receive 0.11 mCi/kg not to exceed 15 mCi. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use to obtain the research information desired. Using the standard way of describing radiation dose, if you/your child received the maximum of 5 scans in 1 year while participating in this study, you/your child will receive a total of up to 24 rem to your/your child's urinary bladder, 16.5 rem to your/your child's heart, and 10.5 rem to your/your child's spleen. All other organs will receive smaller amounts of radiation. Although each organ will receive a different dose, the amount of radiation exposure you/your child will receive from these procedures is equal to a uniform whole-body exposure of up to 5.1rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is slightly above the dose guideline established by the NIH Radiation Safety Committee for research adult

subjects and exceeds the guideline for children. The guideline for adults is for an effective dose not to exceed 5 rem received per year and for children is 0.5 rem per year. For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that you/your child will receive from this research is about the same amount you/your child would normally receive in 17 years from these natural sources. If you/your child would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called *An Introduction to Radiation for NIH Research Subjects.*

The effects of radiation exposure on humans have been studied for more than 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you/your child will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose – even low doses such as those received during this research

A possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in the chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is estimated at 0.2 percent. Therefore, the total risk of a fatal cancer may be estimated to increase from 25 percent to approximately 25.2 percent. This change in risk is small and cannot be measured directly. Compared with other everyday risks, such as flying in an airplane or driving a car, this increase is considered slight. **Please tell you/your child's doctor if you/your child have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation.** This way we can make sure that you/your child will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into you/your child's body.

PET scanning would be scheduled at the baseline prior to starting therapy, and at 1, 6, 12, and 24 months post-transplant. Since these scans would be done solely for the research purposes you can opt out from doing these (see below and sign).

<u>If you are 18 years or older please circle below and initial if you agree or disagree to undergo routine PET scans solely for research purposes. This research procedure is not offered to patients younger than age 18:</u>
:

Agree: Disagree:

Initials: Initials:

Blood sampling*:* For medical management, you/your child will be asked to give blood samples multiple times before, during, and after your/your child's treatments. The blood samples (about 1 to 5 tablespoons each time) are not expected to produce any important decrease in the total amount of blood in your/your child's body. These may be collected by simple venipuncture (needle-stick) from a vein in your/your child's arm or central catheter. Side effects may include pain at the site, bruising, and rarely, bleeding or infection. Some patients can experience light-headedness or fainting during insertion of the needle. These samples collected will be used both for monitoring your/your child's medical condition and for research purposes. Every effort will be made to monitor the total amount of blood volume drawn to avoid exceeding 450 ml (one pint) over any six-week period.

Potential Benefits of Participation

As a participant in this study, you/your child will receive evaluation and treatment of your/your child's systemic lupus. All of the evaluations, tests, and treatments that you/your child receive at the NIH will be free of charge to you/your child. The chemotherapy and drugs you/your child receive are likely to cause major improvement in your/your child's disease, and disappearance of your/your child's symptoms. It is unlikely that the treatment will result in a permanent cure by itself. The autologous stem cell transplantation procedure may however improve the chance that your/your child's disease will enter into a very long remission. However, you/your child should understand that this cannot be guaranteed. You/your child may not directly benefit from this treatment but your/your child's participation may contribute to advances in the understanding and development of new and better treatment of systemic lupus in the future.

Research Subject's Rights

Participation in this research study is voluntary. You/your child may stop your/your child's participation at any time. You/your child must notify the investigator of your/your child's decision to withdraw so you/your child can be correctly advised about medication safety. Some medications cannot be abruptly stopped. There are no penalties for withdrawing from the study. You/your child will be given a copy of this consent for your/your child's records. We encourage you/your child to ask our staff any questions that you/your child have.

New Information

You/your child will be notified of any significant new findings that develop during the course of this research study that may affect you/your child or your/your child's willingness to continue participation.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. : . If you/your child have any problems or questions about this study, or about your/your child's rights as a research participant, or about any research-related injury, contact the Principal Investigator, Steven Pavletic MD; Building 10, Room 12S241, Telephone: 301-231-0543. Paging operator 24hrs/day: 301-496-1211. Another researcher you/your child may call is: Gabor Illei, MD, at 301-496-5236.

You may also call the Clinical Center Patient Representative at 301-496-2626.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)
The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM OCTOBER 31, 2005 THROUGH APRIL 30, 2006.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____