Division of Blood and Marrow Transplantation and Cellular Therapies
4401 Penn Avenue
Pittsburgh, Pennsylvania 15224

Child Informed Consent and HIPAA Authorization Form for Participation in a Research Study

TITLE: Bilateral Orthotopic Lung Transplant in Tandem with CD3 and CD19+ Cell Depleted Bone Marrow Transplant from Partially HLA-Matched Cadaveric Donors (RTB-003)

Investigator: Paul Szabolcs, MD, Professor of Pediatrics
John McDyer, MD

Sub-Investigators: [redacted]

Phone Numbers: [redacted] (Monday-Friday, 8 am to 5 pm only)
[redacted] (24-Hour contact, ask for the BMT Fellow on call)

Source of Support: NIAID Cooperative Agreement

YOUR PARTICIPATION IS VOLUNTARY

We will explain this research study to you and your parent/guardian. You may ask questions.

- Taking part in this study is your decision but requires parent/guardian approval.
- You may change your mind at any time.
- You will be given a copy of this consent form for your records.

KEY INFORMATION ABOUT THE STUDY

This document contains information that will help you/your child decide whether to take part in a research study. We encourage you to read the entire document. All the information is important, but here are some key points to help you understand the study.

- This study is a new treatment approach for patients who have both severe lung disease ("end stage lung disease") and a severe immunodeficiency ("primary immunodeficiency").
- Patients who qualify for this study are typically not candidates for standard lung transplant due to their immunodeficiency. Otherwise, lung transplant would be an option to treat this lung disease.
- Patients who qualify for this study are not candidates for a bone marrow transplant without the lung transplant. Bone marrow transplant would otherwise be an option to treat the immunodeficiency.
- If a suitable donor is found, the first transplant is a double lung transplant. A few months after the lung transplant surgery, a bone marrow is given if you still qualify.

- The bone marrow transplant is investigational. The study doctor removes certain types of white blood cells from the donor bone marrow before giving it to the participant. Removing these cells may reduce complications such as graft versus host disease after the bone marrow transplant.
- Not all participants will qualify for the bone marrow transplant mainly due to complications from the lung surgery or poor lung function.
- If the bone marrow transplant is successful, the new "engrafted" immune cells from the bone marrow may gradually replace the original immune system and treat the original immunodeficiency disease.
- Several months after the bone marrow transplant, the team will evaluate whether the immunosuppressive medications can be slowly lowered and eventually stopped.
- During the time immunosuppressive medication doses are lowered, additional blood tests will be done to make sure there are no issues, such as lung rejection or graft versus host disease (more detail is provided later in the consent).
- Participants who do not qualify for the bone marrow transplant will be put on a medication regimen to help prevent infection and keep the lungs as healthy as possible.
- Both lung and bone marrow transplantation are complex medical procedures that require frequent visits to the study center.
- Visits to the study center involve many tests and procedures to monitor your transplant(s). This includes pulmonary function tests, bronchoscopies, lung transplant biopsies, and bone marrow biopsies.
- There are many risks associated with both lung and bone marrow transplantation. Please take the time to read through the risk section of this consent so that you fully understand all the risks.
- You can choose not to participate in this study and continue with supportive/comfort care to manage the symptoms of both the immune deficiency and lung disease together.

DESCRIPTION (for the parent)
Your child is being asked to participate in this research trial because he or she has developed lung problems as a result of immune deficiency and is not eligible for a lung transplant because of that and is not eligible for a bone marrow transplant because he or she would not be able to tolerate the drugs, chemotherapy and radiation that would be administered. Your child may, however, be able to have both, a double lung transplant and bone marrow transplant, if he or she joins this research study.

The investigator of this study (the study doctor) has developed a new procedure that will allow patients who have both immune diseases and lung diseases to have both the lung and bone marrow transplants. This research study is to evaluate and document how patients do during and after both procedures. From this information, the study doctor is hoping to show that the combination of lung and bone marrow transplantation is safe and effective so that one day the combination can become the standard care for this condition. Approximately 30 patients will be consented in order to enroll 8 patients (who receive both BOLT and BMT) to take part in this research study at the Children's Hospital of Pittsburgh of UPMC.

Participants in this study will have both a double lung transplant (**BOLT**) and a bone marrow stem cell transplant (**BMT**). Your child would receive the lung transplant first, and then at least 8 weeks (and possibly several months) later, after recovering from the lung transplant, would begin preparations for the bone marrow transplant.

Your child will receive a "reduced intensity" type of bone marrow transplant. Researchers will remove T-lymphocytes and B-lymphocytes, two kinds of white blood cells that can attack other body cells if they are sick or foreign. There is more information on this topic later in this consent form.

The use of this type of bone marrow transplantation after a double lung transplant is investigational. The word "investigational" in this case means that the use of this type of bone marrow transplantation to treat immune deficiency after a double lung transplant is still being tested in research studies and is not the standard of care. Bone marrow transplantation is a procedure where the stem cells in your child's blood and bone marrow are replaced by stem cells from a "healthy" donor, in this case a deceased donor who does not have any diseases such as cancer or hepatitis.

If you agree to allow your child to participate in this study, your child will receive stem cells from an unrelated donor whose bone marrow is not identically matched to your child's. The bone marrow and lungs will come from the same donor and be taken from the donor at the same time. When a donor becomes available, only certain study doctors can go out and collect the bone from the donor. This means that if a study doctor is not going to be available for a brief period of time, your child will not be active on the list during that time. The the bone marrow cells will then be processed to remove T and B lymphocytes and then the marrow will be frozen. There is a risk that graft-versus-host disease (GVHD) might occur after the bone marrow transplant. This means that certain cells from the donor, called T-cells, may see your child's cells as "foreign" and attack and destroy your child's cells. The donor's cells are the "graft" cells and your child's cells are the "host" cells. GVHD may be mild to severe, and can affect your child's skin, gut, and/or liver. Very severe GVHD may not respond to treatment and may result in death.

The investigators in this study are able to remove the T- and B- lymphocytes from the bone marrow before your child would receive it. using an instrument called the CliniMACS®. As the liquid marrow sample runs through the CliniMACS® instrument, the instrument identifies the T- and B-lymphocytes and removes them from the marrow. We intend to remove more than ninety-nine percent of all T- and B- lymphocytes from the donor's bone marrow and lower the chances of GVHD occurring. Bone marrow grafts modified using this technique are considered investigational, by the Food and Drug Administration (FDA). Patients who have such a bone marrow transplant may reject the donor cells, meaning that your child's body may not allow the donor's stem cells to grow and replace some of his or her bone marrow. Removal of GVHD-causing T- and B-lymphocytes may also increase the chances that your child's immune deficiency disease may not be corrected after the bone marrow transplant. Rejection of the donor graft could potentially result in death if your child's own marrow does not recover. However, failure of engraftment will more likely result in your child's own marrow growing back. In this case, there would be no beneficial effect on your child's immune deficiency disorder.

The double lung transplant (BOLT) is major surgery – and will require weeks of healing. The bone marrow transplant (BMT) itself is routinely given like a blood transfusion; however, there are several weeks of needed preparation prior to the BMT, which may make your child tired or not feel good for a few weeks afterwards. In addition, the daily medications – especially after BOLT and after BMT-- can be complicated. Frequent testing after BOLT and BMT is typical, in order to try to identify serious problems that can develop after these major treatments. If the BOLT surgery is successful, you may start to notice improvements with your child's lungs. However, for people with

immunodeficiencies like your child, it is expected that this improvement will likely start to worsen in approximately a year or less, unless BMT can successfully treat the immunodeficiency.

Major complications of BOLT and BMT are possible, and frequent and extensive testing and treatments are typically required to try to make BOLT and BMT work well. Some of the possible complications of BOLT or BMT have effective treatments. Other possible complications of BOLT or BMT can be life-threatening. Due to the risk of complications, it is possible that your child receives the BOLT and then does not qualify for BMT. Two of the main reasons for this are:

- The donor bone marrow cells may not be suitable. This is because the lung transplant needs to be completed quickly, before the processing and testing of the bone marrow is finished.
- Your child may experience new or worsening health problems after the lung transplant that mean you no longer qualify for BMT.

If your child does not get a BMT or if the BMT is not successful, the study doctors will work with you to attempt to keep your child as healthy as possible for as long as possible. You will need to take medications to prevent your body from rejecting the lungs. These medications are needed, but can cause complications, such as reducing your ability to fight infection.

PROCEDURES (for the child)
If you decide to take part in this experimental treatment, you and your parent/guardian first will be asked to sign and date this consent form. You will have the following examinations, tests or procedures to determine whether you can be included in the treatment plan and if you are able to receive a transplant.

SCREENING

- Medical history
- Physical examination
- Pregnancy test for girls who are at least 10 years old or who have begun puberty-related changes
- Blood tests to determine whether you have had prior illness such as HIV, hepatitis and other viral illness
- Heart, lung and kidney function tests
- Immune function tests
- Blood sample for research purposes (blood samples will be collected pre-BOLT as well as during the duration of the entire study)
- Bone marrow sample (before bone marrow transplant)

After these screening procedures are done, your doctor will tell you if you are eligible for this research study. If you are eligible, the following steps will happen at the times described.

STUDY PROCEDURES
Preparation for the Lung Transplant
Rituximab may be given before the lung transplant if you have any B cells in your blood. It is given to prevent post-transplant lymphoproliferative disorder (PTLD) which is a type of cancer that can occur after transplant. In addition, Rituximab may prevent sensitization, where you develop antibodies which attack the new lungs.

Lung Transplant

The lung transplant will occur just as it normally would if you were getting a lung transplant outside of a research study. Your child will receive medications after transplant in order to prevent their body from rejecting the new lungs. These are called immunosuppressive medications. Prior to the lung transplant, your child will receive an "induction" medication, which helps to prevent acute rejection after transplant. Basiliximab is the typical induction medication. The ongoing immunosuppressive medications your child will receive are considered standard for lung transplant and may include tacrolimus, mycophenolate mofetil, and steroids.

You will also take medications in order to prevent infections, since the immunosuppressive medications make it harder to fight infection, especially with your existing immune deficiency.

Post-lung transplant follow-up and care
After the lung transplant, all of the follow-up tests and care you will receive is considered routine standard of care and may include the following: physical examinations, bronchoscopies, pulmonary function tests, chest x-rays and blood draws. Part of what is collected will be used for this study. At the same time as your routinely scheduled bronchoscopies we will collect approximately 3 tablespoons of blood. During the bronchoscopy, fluid will be squirted into a small part of your lungs and then collected as part of your routine care. A portion of this fluid not needed for clinical purposes will be used for research testing. In addition, cells and microbiological material from your lungs will be collected for research purposes using a specialized flexible little brush.

Preparation for Bone Marrow Transplant (at least 8 weeks after the lung transplant)
Before you can be cleared to receive the bone marrow transplant, the study team must ensure that you are still eligible. This includes a bronchoscopy and pulmonary function tests to make sure there is no lung rejection and that your new lungs are functioning well. In addition, blood will be drawn and tested to make sure there are no problems with your kidney and liver and that you are healthy enough to move forward. Imaging of your head, neck, chest and pelvis will be done to make sure there are no problems or signs of infection.

Once the study team reviews all of these factors satisfactorily, you can be cleared to begin bone marrow conditioning. The bone marrow conditioning will help prepare your body so the new bone marrow will work properly. For several weeks during and after conditioning, it will be harder for your body to fight infection. For much of this time, you will need to take additional medicines to prevent or treat infections. You and the clinic staff will need to be alert for infection during the conditioning period and in the first weeks or months after BMT. If the study team detects signs of infection or complications, they may pause the bone marrow conditioning treatment.

Before conditioning begins, a sample of bone marrow will be collected in order to monitor your bone marrow graft after transplant. In addition, some of the medicines given to you as a part of the bone marrow conditioning need to be given intravenously, meaning directly into a vein. You will have a central line placed, which is a thin, long tube inserted into a large vein typically in your arm or chest. This can stay in place for several weeks in order to give you medicines before your BMT as well as the bone marrow infusion and certain medicines after your BMT.

The following are approximate times for administering before the bone marrow transplant:
*4 weeks before, you will receive the drug, Hydroxyurea, by mouth;
*4 weeks before (and one month after), you will receive Rituximab, a medicine which may prevent sensitization and lower the risk of PTLD (Post-Transplant Lymphoproliferative Disorder), which is a

type of cancer that can occur after lung transplants and bone marrow transplants
*3 weeks before (if you experienced lung rejection that required treatment), you will be given 2 daily doses of the immunosuppressive drug, Alemtuzumab, also known as Campath-1H;
*14 days before (if you have **not** had any lung rejection that required treatment), you will be given the immunosuppressive drug, Alemtuzumab, also known as Campath-1H;

*3 days before, you will receive 3 daily doses of Antithymocyte Globulin (ATG), another drug to suppress the immune system;
*Two days before, you will receive the chemotherapy drug, Thiotepa;
* One day before, you will receive one dose of Total Body Irradiation (TBI) with shielding (a protective cover for the chest so that the chest is exposed to significantly less radiation) of your lungs. The lungs will not be shielded if you have had lung rejection that required treatment.

Bone Marrow Transplant day
After the conditioning regimen described above, you will receive the T-cell depleted bone marrow transplant as the source of stem cells. The bone marrow will be given by IV infusion (letting a liquid substance flow into a vein using gravity). The infusion should take about 1-3 hours depending on the volume. An allergic-type reaction may develop which may include hives, chills, and rapid pulse or heartbeat. Mild elevations in blood pressure are frequently seen. Rarely, a serious allergic reaction called anaphylaxis could also develop which might include shortness of breath, rash, wheezing, and low blood pressure. Please let the clinic staff know if you are feeling any discomfort during the procedures.

Post-BMT follow-up and care
To speed the recovery of blood cells as much as possible you will receive granulocyte-colony-stimulating factor (G-CSF or Neupogen). G-CSF is a hormone that tells the bone marrow to make white blood cells (cells that help fight infection). You will start receiving growth factor the day of transplant and will continue to receive it daily until your white blood cell count recovers.

If you have an infection after the BMT that does not get better with medicine and/or your white blood cell count is still very low, your doctor may give you a granulocyte infusion. Granulocytes are white blood cells that are a part of the immune system which fight against infection. This infusion is given through your IV, and will last at least 2 hours or longer. You will be monitored closely during and after the infusion period.
After bone marrow transplant, you will be watched very closely. You will have physical examinations and blood tests to monitor your health and evaluate how the donor marrow graft is working. These are all routine standard care for anyone who has a bone marrow transplant. As part of this experimental treatment plan, you will have research blood (up to 5 tablespoons) samples drawn to evaluate the function of your immune system around months 1, 2, 3, 6, 9, and then at years 1, 1 ½ and 2 post-BMT. A chest X-ray will be performed 6 months after the bone marrow transplant. These samples will be collected to see how your immune system is working and to look for any markers of rejection and graft-versus-host-disease.

You will be discharged from the hospital when you doctor feels you are ready. At first, you will need to visit the bone marrow transplant clinic several times a week for checkups. Eventually, the visits will be less frequent. Blood tests other than those mentioned above may also be necessary. Your doctor will make this decision.

If, after your child's bone marrow transplant, they have an issue with engraftment or other complication(s) they may be able to have a donor leukocyte infusion (DLI or 'boost') at any time post-bone marrow transplant. The DLI may be up to 5% of donor stem cells from the initial bone marrow transplant prior to removing the T- and B-lymphocytes. It will be stored separately for future use in case you need them. You and/or your child will be asked to indicate at the end of this consent form if you or your child would like to have this optional up to 5% of the donor stem cells collected and stored for future use. If the investigator and/or a sub-investigator on this study determine your child may need this 'boost', they will explain how this may be of benefit to you child.

Follow up as a part of the study will last two years following bone marrow transplant but you will be followed indefinitely by your transplant doctor or another doctor who is familiar with late complications that may arise from transplantation.

You will also have other tests performed after your bone marrow transplant to monitor your overall health, as well as your transplanted lungs and bone marrow. These include:

- Physical exam
- Lung function tests
- Bronchoscopies
- Chest X-rays
- EKG and Echocardiogram (ultrasound of the heart)
- Endocrine tests
- Blood cell counts
- Kidney and liver tests
- Chimerism analysis (presence of both donor and recipient immune cells in your body)
- Eye and dental exams

Immunosuppression (IS) Withdrawal

Your doctor will consider taking you off your immunosuppressive medications 9 months after your bone marrow transplant (and not less than a year following your lung transplant) if the bone marrow transplant was successful. This means that you are making enough donor stem cells, have not had any GVHD or lung rejection in the past 3 months. If your doctor does take you off your immunosuppressive medications, this will be done slowly over several weeks and you will have more frequent lung function and blood tests during this time to make sure there are no signs of rejection.

DURATION OF THE TREATMENT

Your doctor will follow you for the purpose of this study for a total of 2 years. You may be asked to participate in long-term follow-up after 2 years but that will be a separate study. Please notify your bone marrow transplant doctor if you move or change your primary care doctor so that we will be able to obtain all the information described in this consent form.

RISKS BOLT

The lung transplant is occurring just as it normally would if you were not on a research study. However, due to your child's underlying immune deficiency and the immunosuppressive medicines needed to prevent rejection after lung transplant, there is a higher risk of complications, such as infection and cancer. The study doctor will give your child medications to prevent certain types of infections that can occur when your immune system is suppressed. However, if your child does not receive the BMT after lung transplant and/or the BMT is not successful, this is likely to lower the

chances that your child will survive long term.

Bronchoscopies

You will not undergo stand-alone research bronchoscopies, therefore the risks below will be incurred regardless of study participation as all lung transplant patients have bronchoscopies to monitor the health of their lungs. The most common risks associated with bronchoscopy include minor bleeding, limited to the area of the bronchoscope (the thin tube inserted into your nose or mouth and into your lungs), sore throat, cough, fever, fatigue, and/or mild hoarseness. These are infrequent and usually disappear by the next day. Additionally there are risks associated with medications given during the procedure. Less frequent but serious risks of bronchoscopy are a change in heart rhythm, respiratory arrest requiring intubation, bleeding that requires transfusion, or extremely rarely death (less than 1/100,000). As a precaution, heart rhythm, pulse rate, blood pressure and blood oxygenation will be monitored. Patients will be given additional oxygen during the procedure. There are no long-term hazards of these procedures and no danger of altering the lungs' normal functions. After the bronchoscopy, patients will continue to be monitored closely by the medical staff, and allowed to fully recover from the medications that were given at the start of the procedure. These risks are associated with the bronchoscopy procedure, not the additional fluid sample collected for this study. There is no data on the risk of having an additional lung fluid sample collected. As a precaution, the research sample will only be collected in patients who are tolerating the bronchoscopy. The research BAL sample involves inserting saline and then sucking it out of the lungs along with lung secretions.

Risks Associated with the Medications

Basiliximab (*Simulect®)*

Basiliximab is the typical induction medication at the time of lung transplant. The most common side effects associated with this drug are gastrointestinal symptoms (constipation, nausea, abdominal pain, vomiting, diarrhea, indigestion), redness at the injection site, respiratory symptoms (stuffy nose, sore throat, upper respiratory tract infection), acne, sleep problems (insomnia), headache, cardiovascular symptoms (swelling in your hands, ankles, or feet, high or low potassium levels, high blood pressure), high blood sugars, tremors/shaking, and urinary tract infection .

Less common side effects may include chest pain, heart arrhythmia, difficulty breathing, bronchitis, fatigue, sepsis, gastrointestinal bleeding, joint and muscle pain, hypersensitivity reaction, anxiety, depression, skin irritation and rashes.

Mycophenolic Acid (CellCept®)

Use of mycophenolic acid during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. You (if sexually active) must agree to use birth control during the study. We will discuss acceptable methods of birth control.

Tacrolimus (FK 506)

Tacrolimus will be started at the time of lung transplant and will be continued through the BMT conditioning and post-transplant period. Tacrolimus therapy can produce many side effects. These mainly affect the urinary system and the nervous system. Possible side effects with Tacrolimus are urinary symptoms (pain or difficulty passing urine, frequent urination), fever or chills, respiratory symptoms (cough, sore throat, difficulty breathing, wheezing), decreased red blood cells with unusual weakness or tiredness, fainting spells, lightheadedness, blurred vision, increased sensitivity of the eyes to light, burning or tingling in the hands or feet, , increased thirst or hunger, ringing in the

ears, skin rash or itching (hives), seizures (convulsions), stomach, back or general pain, swelling of the feet or legs, unusual or sudden weight gain, and yellowing of skin or eyes.

Alemtuzumab (Campath-1H)
Cardiovascular symptoms (chest pain, low or high blood pressure, swelling of the hands and feet, fast heartbeat, dizziness), gastrointestinal symptoms (abdominal pain, anorexia, constipation, diarrhea, indigestion, nausea, vomiting), respiratory symptoms (sore throat, inflammation of the airway or lungs, spasm in the lungs, cough, shortness of breath), depression, drug-related fever, chills, strange feelings in your skin, like a burning sensation, fatigue, headache, insomnia, feeling unwell, sleepiness, suddenly feeling hot or cold, itchiness, skin discolorations, rash, hives, inflammation of the skin inside of the mouth and mucous membranes, anemia, low blood cell counts that can be severe, infection, insufficiently- functioning bone marrow, abnormal proteins in the red blood cells, back pain, muscle pain, tremor (involuntary twitching or jerking movement), weakness, excessive sweating.

Rare but important or life-threatening: Abnormally high acidity of the body tissues, acute kidney failure, agranulocytosis (a severe decrease in the white blood cells that fight infection which can cause sores of the mucous membranes and skin), allergy-like reactions, chest pain, swelling of the outer and inner layers of the skin, irregular stops in urination, fluid buildup in the abdominal cavity, asthma, abnormal cell growth in the bone marrow and/or non-functioning bone marrow, cardiac arrest, heart failure, bleeding in the brain or skull, inflammation of the lining of the brain and/or spinal cord, coma, blood clots in the legs (deep vein thrombosis), small clots throughout the blood vessels, bleeding in the stomach or intestines, anemia, coughing up blood, liver failure, overactive thyroid gland, decreased levels of oxygen in the tissues of the body, inflammation of the lung tissue, abnormal holes in the intestine, heart attack, inflammation of the pancreas, paralysis, stomach ulcer, inflammation of the membrane that covers the heart or the abdominal organs, air in the chest cavity, polymyositis (an inflammatory disease of the muscles), progressive multifocal leukoencephalopathy (a viral disease affecting the brain), pseudomembranous colitis (an intestinal infection), swelling, hardening of, or clots in the lungs, kidney dysfunction, possibly due to chemicals, abnormal lung function, possibly causing an abnormally high alkalinity of the body tissues, secondary leukemia, seizure (grand mal), tissue death in the spleen, wheezing, fainting, worsening of some blood cancers, increased platelets in the bloodstream, inflammation of the blood vessels with possible clots, irregular heartbeat, malignant lymphoma, non-functioning bone marrow, meningitis, bleeding in the brain.

Hydroxyurea
Anorexia, constipation, diarrhea, gastrointestinal irritation and inflammation, nausea, pancreatitis, inflammation of the skin inside of the mouth, vomiting, insufficient bone marrow functioning resulting in decreased blood cell counts and changes to the shapes of blood cell.

Infrequent risks: Swelling, chills, disorientation, dizziness, drowsiness, fever, hallucinations, headache, feeling unwell, seizure, hair loss, skin redness including of the face, inflammation of the muscles and skin, skin discoloration, rash, nail changes, skin changes such as ulcers, wasting, scaling, and tissue death, skin cancer, gangrene, elevated levels of uric acid in the blood, painful urination, elevated levels of liver enzymes, liver damage, nerve damage in the hands and feet, weakness, increased blood levels of kidney chemistries, kidney damage, scarring of the lungs, changes to the tissue in the lungs that let air pass through the cells abnormally, shortness of breath, skin cancer, secondary leukemias.

Thiotepa
Chills, dizziness, fatigue, fever, headache, hair loss, skin discoloration, skin inflammation, rash, hives, females' menstrual periods may stop, males may have difficulty making sperm, abdominal pain, anorexia, nausea, vomiting, difficulty or pain while urinating, anemia, bleeding, low white blood cell count, low platelet count, injection site pain, weakness, blurred vision, inflammation or redness of the lining of the eye, blood in the urine, asthma, nosebleeds, throat swelling, wheezing, allergic reaction, anaphylactic shock (a severe allergic reaction), infection.

Rare but important or life-threatening: Acute myeloid leukemia (AML), inflammation of the lining of the bladder, myelodysplastic syndrome (abnormal blood cell counts due to poorly-functioning bone marrow).

Antithymocyte Globulin (ATG)
Common risks: Low blood pressure, chills, fever, itchiness, rash, wheezing, low white blood cell and platelet count, protein in the urine, abnormal kidney function tests, anaphylactic reaction (a severe allergic reaction), serum sickness (an allergic reaction to certain substances in the blood).

Infrequent risks: Fast heart rate, irregular heartbeat, chest pain, swelling, heart failure, high blood pressure, inflammation of the wall of the heart, agitation, headache, tiredness, lightheadedness, listlessness, seizure, changes in the brain due to a viral infection, hives, diarrhea, nausea, vomiting, inflammation of the lining of the mouth, enlargement of the liver and spleen, abnormal liver function tests, burning sensation in the soles of the feet and palms of the hands, injection site reactions (pain, redness, swelling), inflammation of a vein, with or without a clot in the vein, aches, painful joints, back pain, joint stiffness, muscle pain, swelling around the eyes, shortness of breath, fluid buildup in the chest cavity, respiratory distress, excessive sweating, swollen lymph nodes, night sweats, viral infection.

Rare but important or life-threatening: Abdominal pain, acute kidney failure, anaphylactoid reaction, anemia, abnormal cell growth, irregular stops in breathing, confusion, cough, blood clots in the legs (deep vein thrombosis or in the kidney), disorientation, dizziness, abnormally high or low levels of blood cells, stomach pain, nosebleeds, redness of the skin, faintness, flank pain, bleeding and/or perforation of the stomach and/or intestines, red blood cell destruction, herpes simplex reactivation, hiccups, high blood sugar, obstruction of the large veins in the abdomen, infection, twitching, kidney enlarged/ruptured, spasm in the throat, feeling unwell, tingling sensation, swelling in the lungs, stiffness, sore mouth/throat, fast heartbeat, death of the skin cells, tremor, inflammation of the blood vessels, viral hepatitis, weakness, non-healing wounds.

Intravenous Gamma Globulin (IVIG)
Common risks: Sudden hot sensations of or color draining from the face, chills, fever, feeling unwell, nausea, back pain.

Infrequent risks: Chest pain, low blood pressure, fast heart rate, clots in the blood vessels that could travel to the lungs, anxiety, inflammation of the lining of the brain and/or spinal cord, dizziness, headache, irritability, lightheadedness, feeling unwell, seizures, skin inflammation that can progress to oozing, crusted lesions (eczema), redness of the skin, itchiness, hives, abdominal pain, inflammation of the lining of the stomach and/or intestines (gastroenteritis), toothache, vomiting, anemia, temporarily low white blood cell count, joint pain, muscle pain, inflammation of the lining

of the eye, acute kidney failure, acute respiratory distress syndrome, difficulty breathing, swelling of the lungs, tightness in the chest, transfusion-related acute lung injury, excessive sweating, hypersensitivity reactions.

Rare: Irregular stops in breathing, Acute Respiratory Distress Syndrome (ARDS), worsening of autoimmune pure red cell aplasia (PRCA) exacerbation, pneumonia of the lung branches, spasm in the lungs, skin inflammation with blisters, cardiac arrest, chest pain, coma, abnormal proteins in the red blood cells, loss of oxygen to the skin causing a bluish color, skin detachment, rash with red lesions, liver dysfunction, decreased oxygen in the bloodstream, leukopenia, loss of consciousness, decrease in all types of blood cells, rash, blood clot that travels to the lungs, seizure, death of the skin cells, tremor, failure of the blood vessels to distribute blood effectively.

Rituximab (Rituxan)
Common risks: Low blood pressure, fever, headache, chills, dizziness, itchiness, rash, hives, nausea, joint pain, muscle pain, weakness, runny nose.

Infrequent risks: Sudden hot sensation, high blood pressure, swelling of the skin of the hands and feet, anxiety, fatigue, insomnia, migraine, pain, swelling of the outer and inner layers of the skin, high sugar levels in the bloodstream, abdominal pain, diarrhea, indigestion, vomiting, weight gain, anemia, decreased numbers of blood cells in the bloodstream, possibly with a fever, increased liver enzymes, back pain, muscle spasm, abnormal functioning of the nerves, tingling of the skin, spasm in the lungs, cough, shortness of breath, nosebleeds, sinus inflammation, throat irritation, upper respiratory tract infection, infusion-related reactions, infection, night sweats, abnormal antibodies in the blood.

Rare but important or life-threatening: Acute kidney failure, anaphylactoid reaction/anaphylaxis, angina, anemia, Acute Respiratory Distress Syndrome (ARDS), irregular heartbeat, perforation (holes) of the stomach, intestines or bowels, bronchiolitis obliterans (inflammation and thickening of the lung tissue), heart failure, inflammation of the brain, fatal infusion-related reactions, hepatitis, anemia, liver failure, problems with the proteins in the blood, red blood cells that don't mature and therefore don't work properly, decreased levels of oxygen in the tissues of the body, inflammation of the lung tissue, swelling of the throat, dermatitis (a skin condition), lupus-like syndrome (an immune syndrome that mimics lupus), non-functioning bone marrow, heart attack (which could cause shock), irritation of the skin and/or mucous membranes, low blood cell count, inflammation of the eye and/or optic nerve, decrease in all types of blood cells, immune disorders, inflammation of the lining of the chest cavity, pneumonia, arthritis, polymyositis (an inflammatory disease of the muscles), viral diseases affecting the brain, kidney toxicity, serum sickness (an allergic reaction to certain substances in the bloodstream), death of the skin cells, abnormal heart rhythms, inflammation of the blood vessels, possibly with a rash, abnormal contraction of the heart muscle, fast heartbeat, blisters on the skin, tuberculosis reactivation, inflammation of the eye, worsening of viral infections, wheezing, Tumor Lysis Syndrome (a condition caused by the sudden release of dead tumor cells into the blood, which can cause chemical imbalances).

Also, a few adults who have received Rituximab have developed PML (Progressive Multi-focal Leukoencephalopathy). This complication leads to brain damage and results in memory loss, problems with thinking, and blindness, which together may lead to death. Some patients who have received Rituxan in combination with chemotherapy have had a virus in their liver become active again. This is called reactivation of the Hepatitis B virus. This can cause severe liver disease (for

example, hepatitis) which can be fatal.

Total Body Irradiation (TBI)

Your child will receive one fraction of total body radiotherapy treatment given in a conventional manner over one day as part of the treatment to prepare you for the bone marrow transplant. Side effects include 1) nausea and vomiting, for which medication will be given; 2) mucositis, an irritation of the lining of the mouth and digestive system, which can lead to mouth pain and ulcers, difficulty swallowing and eating, cramps, and diarrhea; 3) low blood counts, with risks of serious bleeding and infections and the need for transfusions and antibiotics; 4) swelling of the saliva glands, which is mild and usually not painful; 5) fever; 6) temporary redness of the skin, with later darkening of the skin; and 7) late permanent effects, which include cataracts (cloudiness of the eye), growth disturbances, sterility, thyroid or adrenal gland insufficiency, and secondary cancers (cancer tumors at other locations). Occasionally, damage to the lungs, liver, and kidneys can be seen from radiotherapy.

Bone Marrow Transplant Risks

In addition to the intensive pre/post-transplant treatment regimen side effects, the following risks may occur with a bone marrow transplant:

1. Bone marrow depression: Bone marrow depression means decreased blood counts, including red blood cells, white blood cells, and platelets. Until the new bone marrow begins to grow, your child is at risk of developing infections or bleeding. Infections can be treated with antibiotics. Bleeding can be corrected, at least in part, by transfusions. However, there are risks associated with the transfusions of red blood cells and platelets during the post-transplantation period. These risks include fluid overload; serious allergic reactions; and infections, including hepatitis, cytomegalovirus (CMV), and human immunodeficiency virus (HIV), the virus that causes AIDS. All blood products will be screened for these infections in order to reduce the chance that the blood contains these viruses.

   Risks regarding transfusions of blood products: As part of your child's medical treatment, your child will need to receive transfusions of blood products (red blood cells and platelets, plasma or white blood cells). These products come from healthy volunteers from the general population who choose to donate blood for the use of patients such as your child. Blood donors and blood products are carefully screened and tested to minimize the risk of transmitting any infectious disease or problem, but it is impossible to eliminate all risk. Other risks include itching, hives, wheezing, fever, less common risks include allergic reaction, anaphylactic shock, transfusion reaction, immune reaction, fluid overload, hemochromatosis, infection, blood unit labeling errors, recipient identification errors, and blood unit contamination. However, not receiving a transfusion when needed can carry a great risk of serious injury or death.

   While transfusion of autologous blood (your child's own blood) is a service available for patients with less serious illness, it will not be possible to use your child's blood after transplantation. At an additional charge, you may arrange for friends or family members to donate blood for your child, but, since many products must be matched to your child's blood type to be used, blood donated by relatives/friends may not be suitable for your child's use. Therefore, your child will receive blood products from the CHP/PRESBY Transfusion Service. Alternatives to transfusion such as hemoglobin substitutes are not in general use at this time.

2. Graft Failure: The bone marrow may fail to "take" or engraft. This may occur in a significant number of patients, depending on the disease for which your child is being transplanted. It is possible that the new marrow will grow, but not work normally. This will result in low blood counts for a long period of time and your child will be at risk for developing infections or bleeding as described above for bone marrow depression. Blood samples will be taken in the weeks and months after your child's transplant infusion to see how well the donor stem cells are taking in your child's marrow.

3. Graft Versus Host Disease: This condition results from a reaction of the transplanted cells against your child's body and organs. This reaction ranges from a mild skin disorder to severe involvement of the skin, liver, and/or gut. It may be fatal in some children. Your child will be monitored for this complication and given specific treatment to try to prevent it. There are two forms of GVHD: acute (early) and chronic (late).

   Acute GVHD may produce skin rashes, liver disease, diarrhea, and an increased risk of infection. All of these can range in severity from mild to fatal. To confirm the diagnosis of acute GVHD, your child may be required to have a skin biopsy or endoscopy. Your child may be treated with high doses of corticosteroids and additional immunosuppressive agents.

   Acute GVHD can persist and become Chronic GVHD. Chronic GVHD can also appear in people without prior acute GVHD. Chronic GVHD may also produce skin rashes, liver disease, diarrhea, and an increased risk of infection. Chronic GVHD may be mild and respond to drugs that suppress the immune system, or it could be very severe. It may also last for over a year.

   In an attempt to prevent or minimize the severity of graft-versus-host disease (GvHD), your child will receive Tacrolimus beginning before the bone marrow transplant and continuing post-transplant.

   GVHD may also occur from a DLI or "boost" after the initial bone marrow transplant, if needed.

4. Veno-occlusive disease (VOD) of the liver: This is a complication that results from high doses of chemotherapy, or radiation, or both and we think it is unlikely to occur given the doses used in this clinical trial. Patients who suffer this develop jaundice (yellowish skin), liver function abnormalities, abdominal swelling, and abdominal or shoulder pain. These usually occur in the first month after transplant. Veno-occlusive disease can be fatal.

5. Interstitial pneumonia: Some children suffer severe lung problems from either a viral infection called cytomegalovirus (CMV) or a reaction to the chemotherapy given. Interstitial pneumonia can cause inflammation of the lungs. If these complications occur, your child may require oxygen and various medications for treatment. Although treatments are available, this form of pneumonia can be fatal.

6. Recurrence of disease: It is possible that your child's immune deficiency disease is not fully corrected even if donor cell engraftment is documented.

7. Serious infections: Full and complete recovery of your child's immune system may take

several months and possibly even beyond a year or two following successful marrow engraftment. During this time, there is an increased risk of infections. Your child will be prescribed certain medications to reduce the chance of those infections. Preventive treatment is not always effective. If your child has an infection, your child may have to be re-hospitalized after transplant. Infections may be fatal. Fatal complications of infections include life-threatening pneumonia, liver disease, and/or loss of the new bone marrow or lungs.

8. Organ damage: In addition to the complications listed above, it is possible that the bone marrow transplant procedure will result in damage to your child's heart, lungs, kidneys and/or liver. This damage may be mild, moderate or severe. Severe damage may be fatal. Long-term complications from the transplant procedure include the potential for growth problems, hormonal and learning difficulties, and infertility.

9. Genetic Disease Transmission: There is the potential that certain genetic diseases (such as thalassemia or adrenoleukodystrophy) may be passed through the bone marrow transplant. These diseases are very rare, so the risk of this transmission occurring is small.

10. Infectious Disease Transmission: During harvest, microbial contamination may occur. If this were to happen you would be notified and the appropriate antibiotics will be given to eliminate/minimize the risk of infection.

11. There may be risks, discomforts, drug interactions or side effects that are not yet known that may be serious or fatal.

12. There is a risk of unexpected death from complications of treatment, including granulocyte infusions.

White Blood Cell (Granulocyte) Infusion(s)

- Common reactions are typically mild reactions including: rash, itching, fever, chills and headache.
- Less common reactions are more serious and include: respiratory distress or lung injury, exposure to blood borne bacteria or parasites that could result in infection, possible effects on the immune system, which may decrease the body's ability to fight infection, exposure to blood borne viruses such as Hepatitis B and shock.
- Extremely rare side effects are more serious and include: exposure to blood borne viruses such as Hepatitis C and Human Immunodeficiency Virus (HIV), cardiac events such as myocardial infarction (heart attack), and death.

Donor Leukocyte Infusion

The DLI is a small portion (up to 5%) of the original donor stem cell transplant cells that are set aside at the time of your child's transplant. This small portion of cells is labeled with your child's information, frozen, and saved indefinitely until a time that your child might need the DLI. Getting the DLI to your child after the transplant can provide a "boost" to the stem cell transplant cells that are in your child's marrow, but might grow too slowly. Only your child can receive the DLI cells that were saved from his or her original transplant, and your child cannot receive anyone else's DLI

cells. There will be a section at the end of this consent that asks for your permission to reserve up to

5% of the donor stem cells to freeze and save in case a DLI is needed. These cells may never be used unless there is a clinical reason to believe that they would help your child recover faster from a severe infection or would prevent or treat rejection of the new stem cells. The infusion of this unmodified bone marrow will not happen without your written signed consent as these cells could trigger severe graft versus host disease. Removing this small portion of the bone marrow cells should not have any significant negative impact on how well the donor cells "take" in your child's marrow. However, there is a very small chance that the DLI portion, once it's removed from the graft, could be accidentally destroyed in the freezer (i.e. if the electricity fails or the freezer breaks) while it's being stored. If this happens, your child would not receive all of the cells that were collected from your donor. In addition to GVHD, there is a risk of infusion reaction, transmitted disease and/or infection, bone marrow depression, graft failure and engraftment syndrome (described above).

IS Withdrawal
The most serious risk of IS withdrawal is rejection. You could experience rejection of your transplanted lungs and/or GVHD. If you do experience any type of rejection or GVHD, you will receive the appropriate treatment and be restarted on IS at the discretion of your study doctor.

Risks of Central Line Placement
Risks include but are not limited to: bleeding, infection, injury to your arteries and/or lungs, pneumothorax (collapse of lung).

Risks of Blood Draw and IV Insertion
Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Bone Marrow Aspiration Risks
This test may be painful. There is also a small risk of infection or bleeding. The pain normally lessens within minutes to hours.

RISKS TO AN UNBORN CHILD
Because participation in this study may harm a pregnancy, your child and any person with whom your child has sex must use an approved form of birth control for as long as they are taking any medication that may harm a pregnancy, an unborn child or may cause any birth defects. They should discuss with their physician prior to stopping or changing their birth control method. If your child becomes pregnant or fathers a child while in this study, you must tell your child's doctor at once. Also, women must not breast feed while in this study. If your child is a female and able to become pregnant, your child will have a urine or blood test to make sure that she is not pregnant before she is permitted to undergo the experimental procedures. The results of the pregnancy test will be discussed with you and your child. If you or your child has questions, you are encouraged to speak with either the study doctor or your child's personal physician. If your child has reached puberty, and you are concerned about his or her ability to have children in the future and the effects that the drugs that he or she will receive during this study will have on your child's reproductive organs, it is strongly advised that you contact a fertility specialist for more information. Fertility preservation options will vary based upon age, gender, and medical history. The study doctor can explain this option and provide contact information for a fertility specialist if you would like more information.

☐ _____ **Yes**, I understand the above information and confirm my child will use an approved form of contraception.
Initials

☐ not applicable

BENEFITS
It is hoped you will have both, a successful lung transplant to replace your injured lungs and a successful bone marrow transplant to correct your immune deficiency disease, however there are no guarantees. It is possible you may only benefit from a successful lung transplant, only a successful BMT, or you may not benefit from participating in this study at all. The information learned from this study may benefit future patients with immune deficiency and lung disease.

WHAT OTHER CHOICES ARE THERE IF MY CHILD DOES NOT TAKE PART IN THIS STUDY?
The study doctor and/or study staff will talk with you about this study and other options available to you. You may choose not to be in this research study. Other options include:

- Continue getting the standard treatment or care.
- Supportive/comfort care: Since major reversal of the lung disease or immunodeficiency cannot be expected with routine care, the goal is to detect treatable problems. Testing and treatment can be less extensive, since the main goal is to keep your child comfortable and slow down the worsening of their existing lung and other problems.

COSTS
You or your insurance provider will be responsible for the costs related to your medical care, including the drugs used in this treatment. You will not be responsible for the cost associated with manufacturing the investigational bone marrow product. Additional tests may be performed on your blood or tissues to test if you are tolerant to your new lungs and bone marrow. Any tests or procedures performed solely for research will be covered by the study. You or your insurance provide will be responsible for the costs of other tests and FDA-approved medicines used in this research study. These tests and medications are standard of care for the patient undergoing bone marrow transplant or lung transplant. Standard costs include those of your hospitalization, doctor's visits, standard laboratory tests, medications, and the cost of any hospital stays in the bone marrow stem cell unit
Financial counseling services will be available to subjects to address insurance questions prior to consent and throughout study participation.

COMPENSATION
There will be no compensation for your participation in this treatment.

Your child’s data and specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You or your child will not retain any property rights nor will you or your child share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

CONFIDENTIALITY
How will my child’s privacy rights be protected?

Any information about your child obtained from this research will be kept as confidential (private) as possible. All records related to his/her involvement in this research study will be stored in a secure place (a locked file cabinet and/or password and firewall protected computer). Your child's identity on these records will be indicated by a case number rather than by name, and the information linking these case numbers with his/her identity will be kept separate from the research records. If your child's information is shared with other investigators, the information will be de-identified; namely identifiable information such as name and birth dates will be removed. Your child will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

Will this research study involve the use or disclosure of identifiable medical record information?
This research study will involve the recording of past, current and/or future identifiable medical information from your child's hospital and/or other health care provider (for example, the physician's office) records. This information that will be recorded will be limited to information concerning treatment of your child's disease (for example, diagnostic information, lab results, medications, medical history). This information will be used to determine your child's eligibility for this study and to follow his/her response once enrolled in the study.

This research study will result in identifiable information that will be placed into your child's medical records held at UPMC. The nature of the identifiable information resulting from participation in this research study that will be recorded in your medical record includes diagnostic information, lab results, and response to study treatment including adverse events (side effects).

Who will have access to my child's medical information related to its participation in treatment?
In addition to the investigators listed on the first page of this consent form and their research staff, the following individuals will or may have access to identifiable information (which may include identifiable medical record information) related to your child's participation in this research study:

- University of Pittsburgh Office of Research Protections;
- US Food and Drug Administration (FDA);
- Authorized representatives of the UPMC hospitals or other affiliated health care providers;
- National Institute of Allergy and Infectious Diseases (NIAID), NIAID representatives, agents, employees, contractors, and other persons assisting in conducting, monitoring or analyzing the study;
- Other State and Local health authorities;
- Children's Hospital of Pittsburgh will use the clinical data from your child's treatment records for reporting the results of our BMTCT program. The results will be reported to the National Cancer Institute, the International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry (IBMTR/ABMTR), the Pediatric Blood and Marrow Transplant Consortium (PBMTC), the Foundation for the Accreditation of Hematopoietic Cell Therapy (FACT), and the scientific community. No mention of your child's name or any identifying information will appear in any of the reports;
- In unusual cases, the investigators may be required to release your child's treatment information in response to a court order. Physicians may be required under Pennsylvania law to report any suspicion of child abuse to child protection services. If the investigators learn that you or someone with whom your child is involved is in serious danger of potential severe harm, they may need to warn those who are in danger and contact other agencies to ensure safety.

For how long will the investigators be permitted to use and disclose identifiable information related to my child's participation in this research study?
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your child's participation in this research study for a minimum of 7 years after final reporting and publication of the project and for as long (indefinite) as it may take to complete this research study.

May I have access to my child's medical information resulting from participation in this treatment?
In accordance with the Children's Hospital of Pittsburgh's Notice of Privacy Practices document which you have been provided, you are allowed to look at information (including information resulting from participation in this treatment) contained within your child's medical records.

Is my child's participation in this research study voluntary?
Your child's participation in this research study, to include the use and disclosure of his/her identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your child's identifiable information for the purposes described above, he/she will not be allowed, in general, to participate in the research study.) Whether or not you provide consent for your child's participation in this research study will have no effect on your or your child's current or future relationship with the University of Pittsburgh, current or future medical care at a UPMC hospital or affiliated health care provider or current or future relationship with a health care insurance provider.

Your child's doctor may be an investigator in this research study, and as both a doctor and a research

investigator, s/he is interested both in your child's medical care and in the conduct of this research. Before agreeing to allow your child to participate in this research study, or at any time during your child's study participation, you may discuss your child's care with another doctor who is in no way associated with this research project. You are not under any obligation to allow your child to participate in any research study offered by the doctor.

May I stop my child's participation in this treatment?
You have the right to stop your child's participation in this treatment at any time.

If you decide to withdraw your child from this proposed treatment before he/she receives the doses of drugs, we will continue to offer him/her the best available alternative care according to his/her needs and physical condition. However, you should understand that if you withdraw your child from this treatment plan after administration of the chemotherapy but before the infusion of the bone marrow transplant, your child might die. The reason is that he/she would be left without enough cells in the marrow to produce the white blood cells, platelets, and red cells necessary to sustain life.

If you wish to withdraw your child from this research study, please notify the study doctor in writing using the address on page 1 of this consent.

Will the researchers tell me if they learn of new information that could change my willingness to allow my child to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to allow your child to stay in this study. If new information is provided to you after your

child has joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

Could the researchers take my child out of the study even if I want to continue to allow my child to participate?
Yes. There are many reasons why the researchers may need to end your child's participation in the study. Some examples are:

- The researcher believes that it is not in your child's best interest to stay in the study.
- Your child becomes ineligible to participate.
- Your child's condition changes and he/she needs treatment that is not allowed while taking part in the study.
- You and/or your child do not follow instructions from the researchers.
- The study is suspended or canceled.

Will there be any compensation if my child is injured as a result of participating in this treatment?
If you believe that your child has been injured as a result of the research procedures being performed, please contact the Principal Investigator or one of the co-investigators listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to your child by the hospitals of UPMC. If your child's research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not waive any legal rights by signing this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

Storage of Samples
We are planning to store unused samples and information resulting from the analysis of samples of biological specimens (e.g., blood, tissue, bone marrow, and BAL fluid) collected during the course of this study to be used in the future for tests that aren't yet planned. Any research not yet planned will need to be approved by an Institutional Review Board.

We may share your child's de-identified data, including genetic data and samples with other researchers or repositories in the future for research purposes.

This research could include other diseases and may involve research tools such as gene sequencing. Gene sequencing of your child's DNA provides researchers with the code to your genetic material. Genetic tests study an individual's inherited characteristics, found in DNA, which is present in each of the cells of your body. DNA contains information needed to construct and operate the human body.

The risks associated with genetic studies include the potential for a breach of confidentiality which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships and/or result in paternity suits or stigmatization. A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use

your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Some information about a research specimen will always be linked to it. For example, researchers will know the sample is from a lung transplant and bone marrow transplant recipient. Samples will be stored using a coded ID.

The results of tests performed on stored samples or reports resulting from the analysis of your child's samples will not be given to you or your doctor and they will not be put in your child's medical record. They will not identify your child and will not affect their routine medical care.

Samples will be stored at the University of Pittsburgh while the study is ongoing and possibly for years following study completion. You can change your mind at any time and ask to have your child's samples destroyed. This request should be made in writing to the study doctor. If you make this request, all remaining stored samples will be destroyed. However, the results of any previous tests using your stored samples will be used.

VOLUNTARY CONSENT - PARENTAL PERMISSION

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the Human Research Protection Office (HRPO), University of Pittsburgh [redacted] to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

A copy of this consent form will be given to me/my child.

_____
Participant's (Child's) Printed Name

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____	_____
Parent's Name (Print)	Relationship to Participant (Child)

_____	_____	_____
Parent's Signature	Date	Time

_____	_____
Parent's Name (Print)	Relationship to Participant (Child)

_____	_____	_____
Parent's Signature	Date	Time

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study

_____	_____	_____
Signature of Person Obtaining Consent	Date	Time

In addition, by checking and initialing below, I give my permission for the following sample to be collected and stored for future use if necessary:

☐ ____ **Yes**, I consent to remove up to 5% of the donor stem cells from the donor graft. I consent to the storage and future use of these stored cells as a donor lymphocyte infusion (DLI) if my child's bone marrow should need a "boost" after the initial bone marrow transplant. I understand that the stem cells will be stored indefinitely, and can only be used for my child. (check and initial)

☐ ____ **No**, I do not consent to remove up to 5% of the donor stem cells from the donor graft. (check and initial)

CHILD ASSENT

☐ _____ I **DO NOT** believe the child/my child is capable of giving assent for participation.

☐ _____ I **DO** believe the child/my child is capable of giving assent for participation.

_____
Signature of Parents(s) or Guardian(s)

_____
Signature of Parents(s) or Guardian(s)

This research has been explained to me, and I agree to participate.

_____ _____
Signature of Child Participant Date

VERIFICATION OF EXPLANATION
I certify that I have carefully explained the purpose and nature of this research to the subject in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

_____ _____
Signature of Person Obtaining Consent Date

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from one of my parents. I have now reached the age of 18 and I am able to provide direct consent for continued participation in this research study.

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the HRPO, University of Pittsburgh [redacted] to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable

By signing below, I agree to continue my participation in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Signature	Date	Time

INVESTIGATOR'S CERTIFICATION

I certify that the nature and purpose, the potential benefits, and possible risks associated with continued participation in this study have been explained to the above individual and that any questions about this procedure have been answered.

_____	_____	_____
Investigator's Signature	Date	Time

PARENTAL REAFFIRMATION OF CONSENT- BONE MARROW TRANSPLANT

I understand that my child is now moving forward with the next portion of the study, the bone marrow transplant. The risks associated with the bone marrow transplant have been explained to me and are included in this consent form. All of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the HRPO, University of Pittsburgh [redacted]) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

A copy of this consent form will be given to me/my child.

_____
Participant's (Child's) Printed Name

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____	_____
Parent's Name (Print)	Relationship to Participant (Child)

_____	_____	_____
Parent's Signature	Date	Time

_____	_____
Parent's Name (Print)	Relationship to Participant (Child)

_____	_____	_____
Parent's Signature	Date	Time

CERTIFICATION OF REAFFIRMATION CONSENT- BONE MARROW TRANSPLANT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent was signed.

_____	_____	
Printed Name of Person Obtaining Consent	Role in Research Study	
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time

PARENTAL REAFFIRMATION OF CONSENT- IMMUNOSUPPRESSION WITHDRAWAL

I understand that my child is now proceeding with the next portion of the study, immunosuppression withdrawal. The risks associated with the withdrawal of immunosuppression have been explained to me and are included in this consent form. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh [redacted] to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

A copy of this consent form will be given to me/my child.

_____
Participant's (Child's) Printed Name

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____	_____
Parent's Name (Print)	Relationship to Participant (Child)

_____	_____	_____
Parent's Signature	Date	Time

_____	_____
Parent's Name (Print)	Relationship to Participant (Child)

_____	_____	_____
Parent's Signature	Date	Time

CERTIFICATION OF REAFFIRMATION CONSENT-IMMUNOSUPPRESSION WITHDRAWAL

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study

_____	_____	_____
Signature of Person Obtaining Consent	Date	Time