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APPENDIX A

Sample Informed Consents

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A.1 SAMPLE CONSENT FORM FOR PATIENTS WITH MALIGNANT DISEASES

Written Summary of Informed Consent

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

You (your child) are being asked to take part in a clinical research study. Clinical research tries to find better ways to diagnose and treat disease. Taking part in any clinical research involves risks and benefits. You need to understand these risks and benefits to make an informed decision about whether or not to join the study. This process is known as informed consent.

This consent form gives detailed information about the research study which your doctor will discuss with you. Once you understand the study, you will be asked to sign this form if you wish to take part. You will have a copy to keep as a record.

The research study you are being asked to join is:

UNRELATED DONOR UMBILICAL CORD BLOOD AS AN ALTERNATE SOURCE OF STEM CELLS FOR TRANSPLANTATION

PURPOSE OF THE RESEARCH STUDY

You (your child) have been asked to participate in a research study to look at the ability of umbilical cord blood cells from an unrelated donor to serve as a source of stem cells for patients undergoing bone marrow replacement. Stem cells can be thought of as “parent cells” of bone marrow. These “parent cells” make new bone marrow which in turn makes red blood cells, white blood cells, and platelets. These cells are absolutely necessary to live. The main purpose of this study is to determine how well cord blood cells from unrelated donors will grow after transplantation into the patient. This study will also determine the side effects that may result from a transplant using unrelated donor cord blood. You (your child) will be one of approximately 350 patients enrolled in this study.

You (your child) have a disease of the bone marrow which is unlikely to be cured with conventional non-transplant treatment. The best results with bone marrow transplantation are obtained when the donor is a relative who has the same tissue type (HLA-type) as the patient. You (your child) do not have such a donor available. This study will investigate whether or not umbilical cord blood may be used instead of marrow cells.

Umbilical cord blood cells are a readily available source of donor stem cells. These cells are obtained by taking blood from the placenta and umbilical cord of the donor at birth and freezing them for future use. This umbilical cord blood has the potential to replace the diseased cells in your(your child)’s bone marrow that normally make white blood cells, red blood cells and platelets.

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To date, approximately 1000 patients worldwide have been transplanted with umbilical cord blood from unrelated donors. There is no evidence of a difference in long-term bone marrow function between patients who have received umbilical cord blood cells as compared to patients who have received bone marrow. However, the first unrelated cord blood transplant was performed in 1993 and average follow-up is limited.

DESCRIPTION OF THE RESEARCH PROCEDURES

You (your child) will undergo an intensive treatment before transplantation of the unrelated donor umbilical cord blood cells. The intensive treatment is designed to kill any abnormal cells in your (your child's) bone marrow. The treatment will also kill all the normal cells in your (your child's) bone marrow. The treatment will include drugs and may include total body irradiation .

Starting about nine days before transplant, you (your child) will receive total body irradiation and three additional drugs. You (your child) will receive total body irradiation twice per day for four days and once on the fifth day. **If you (your child) are a male and have been diagnosed with Acute Lymphoblastic Leukemia (ALL), you may also receive testicular radiation during this time.** Then, you (your child) will receive the chemotherapy drug cyclophosphamide. The second drug you (your child) will receive is methylprednisolone. This drug will be given by vein for 3 days to suppress your (your child's) immune system. The third drug you (your child) will receive is antithymocyte globulin (ATG). You (your child) will receive this drug by vein for 3 days to further suppress your (your child's) immune system. None of these drugs are considered to be experimental. The risks of this intensive treatment are given below.

During the period of this intensive treatment and until your immune system shows signs of recovery, you (your child) will be isolated in a protective environment. As part of your (your child's) transplant procedure, you (your child) will have a central venous (e.g. Hickman) catheter inserted. This will allow blood to be drawn daily. This will also allow medicine and nutrition to be given daily without having to do several skin punctures. This common procedure is also used for patients receiving marrow transplants.

The umbilical cord blood cells will be given to you (your child) by vein the day following the intensive treatment. These cells will be given to restore normal bone marrow function. The cord blood will be administered in a small transfusion bag through your (your child's) central venous (Hickman) catheter.

Following transplantation, you (your child) will receive two medications to decrease the chance of graft versus host disease (GVHD). GVHD is the reaction of the donor cells against your (your child's) body. On the day before the cord blood transplant, you (your child) will receive the drug cyclosporine to suppress your (your child's) immune system. This will be given in your (your child's) catheter until you (your child) is again able to take medications by mouth. Beginning five days after the transplant, you (your child) will also receive more methylprednisolone. This will also be given through your (your child's) catheter until you (your child) are able to take medications by mouth. Both of these drugs will be reduced over a 3-6 month period after transplantation.

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You (your child) will receive a drug called granulocyte-colony stimulating factor (G-CSF) starting the day of the transplant. G-CSF is believed to help your (your child's) new "parent cells" grow.

After the transplant, it will be necessary to monitor the ability of cord blood cells to grow in your (your child's) body. Your (your child's) doctors will examine your (your child's) blood (2 teaspoons) and bone marrow (1 teaspoon) on days 30, 60, 90, at 6 months, and yearly after transplantation. This is necessary to make sure that the cord blood cells are growing and making new bone marrow.

Your (your child's) doctors will also evaluate the recovery of your (your child's) immune system. This will require a blood sample (2 teaspoons) on days 30, 60, 90, at months 6, 9, 12, 18, 24, and yearly until your (your child's) immune system is normal. Two-three teaspoonful of additional blood may also be taken and used for HLA typing, chimerism assays and storage for future studies. These studies will not directly benefit you (your child) but will hopefully benefit patients in the future.

The blood will be obtained from your (your child's) catheter until the catheter is removed. Afterwards, it will be collected through your (your child's) vein. Bone marrow samples will be removed from your (your child's) hip bones using a needle and syringe. These procedures may cause brief pain to you (your child).

You (your child) will be followed very closely by the transplant doctors for the first year after transplantation. Your (your child's) doctors will then examine you (your child) at least once a year or more often if there are continuing medical problems.

You (your child) may also be asked to give informed consent for participation in other studies. These studies typically deal with prevention and treatment of transplant problems. You (your child) will only be asked to take part if you (your child) are at risk for developing the particular problem related to the study.

DESCRIPTION OF SIDE EFFECTS AND TREATMENT - RISKS

The side effects associated with transplantation can be uncomfortable and in some cases are potentially dangerous, life-threatening, or fatal. Because this is a research study and the treatments are relatively new, there may be additional side effects which are not known or predictable at this time. Both radiation and drugs may lead to an increased chance of malignancy later in life. **As is true with all medication and treatment, other unexpected side effects may occur.** The known or possible side effects of the pre and post-transplant treatments you may receive as part of this study are listed below:

1. **Total body irradiation.** Total body irradiation (TBI) may cause transient nausea and vomiting. Anti-vomiting medications can be given as a treatment. TBI may also cause mucositis, an irritation of the lining of the mouth, esophagus, bowel, and rectum. This can lead to mouth pain and ulcers, difficulty swallowing and eating, cramps, and diarrhea. Swelling of the salivary glands may be another problem. Low blood counts, hair loss, and temporary redness of the skin, with later darkening of the skin may also occur.

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Late effects of TBI include cataracts. Cataracts are cloudiness in the lens of the eye. They can be surgically corrected. There can be interference with normal growth which can sometimes be corrected with hormone replacement. There can be thyroid and adrenal gland insufficiency. This can be treated with hormone replacement. Permanent sterility may occur. A secondary cancer can also occur. Younger children may be at risk for permanent interference with mental functioning.

2. **Cyclophosphamide.** The high doses of cyclophosphamide may cause low blood counts, hair loss, mucositis and darkening of the skin, and transient nausea and vomiting. Anti-vomiting medications can be given to treat the transient nausea and vomiting.

Less common side effects include water retention which can be treated with medicines; potentially fatal damage to the lungs or liver or weakening of the heart muscle; bloody urine, for which precautions will be taken but which is occasionally very severe.

3. **Antithymocyte globulin (ATG).** Antithymocyte globulin (ATG) has been associated with fever, feeling weak, joint pains, rash, low blood counts, hemolysis, and breakdown of red cells in the blood. More severe toxicities include hives, difficulty breathing, and low blood pressure (hypotension.)
4. **Cyclosporine.** The possible side effects of cyclosporine include growth of excessive body hair, reddened gums, increased blood pressure, and liver and kidney damage. In rare instances, central nervous system toxicity with tremor, somnolence (sleepiness), confusion, and seizures may occur. These are reversible after stopping the medication. The amount of cyclosporine in the blood will be monitored to keep these problems to a minimum.
5. **Corticosteroids.** Corticosteroids are prednisone (when taken by mouth) and methylprednisolone (when taken by vein). The possible side effects include weight gain and water retention, puffiness of the face, high blood pressure, high blood glucose, bleeding from the stomach and intestines, and personality changes including depression and psychosis. High blood pressure can be treated with medications. High blood glucose can be corrected with insulin.

Although long term corticosteroid administration is not proposed in this study, corticosteroids can be used for treatment of acute and chronic GVHD. Long-term use has been associated with muscle weakness and wasting, cataracts, and suppression of growth in children. It has also been associated with bone thinning. This has sometimes progressed to areas of bone death especially at the knees and hips. In addition, steroids may make you (your child) prone to infections.

6. **Granulocyte-Colony Stimulating Factor (G-CSF).** G-CSF will be used to help regrow the new bone marrow. In general, this drug has few serious side effects. Side effects which have been reported include fever, feeling tired, bone pain, and enlargement of the spleen. Additionally, there is a rare risk of allergic reaction to this drug.

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Busulfan and Melphalan only used on specific patients who do not receive TBI and cyclophosphamide

7. **Busulfan.** Busulfan may cause vomiting, diarrhea, and seizures. Medication will be given to minimize or prevent some of these side effects. Late effects, which are usually temporary, may include hair loss and increased color of the skin (hyper pigmentation.) Some patients may develop a rash. Some patients may develop mouth sores (mucositis). Some patients may develop abnormal function of the liver or lungs which may be mild, moderate, or potentially fatal if severe.
8. **Melphalan.** The major side effects of melphalan include severe suppression of blood counts, nausea, vomiting, mouth and throat sores (mucositis) and diarrhea. Scarring of the lungs (pulmonary fibrosis) has been reported to occur after the use of melphalan. Serious allergic reactions including low blood pressure (hypotension) and heart stoppage (cardiac arrest) following use of this drug also have been reported.

In addition to the intensive pre/post-transplant treatment side effects, the following risks may occur:

1. **Bone marrow depression.** Bone marrow depression means decreased blood counts, including red blood cells, white blood cells, and platelets. Until the new cord blood cells begin to grow, you (your child) are 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.
2. **Graft Failure.** The cord blood may fail to “take” or engraft. This may occur in a significant number of patients, depending on the disease for which you (your child) are being transplanted. It is possible that the cord blood will grow, but not work normally. This will result in low blood counts for a long period of time. Graft failure is typically fatal. Should the graft fail, you (your child) will not have access to additional stem cells from the donor.
3. **Graft-versus-host-disease (GVHD).** This condition results from a reaction of the transplanted cord blood cells against your (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 patients. You (your child) will be monitored for this complication and given specific treatment to prevent and treat it. There are two forms: 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, you (your child) may be required to have a skin biopsy and possibly a liver or

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gut biopsy. The treatment of acute GVHD requires you (your child) to take high doses of corticosteroids. Occasionally, other drugs such as antithymocyte globulin (ATG) are given.

Acute GVHD can persist and become chronic GVHD. Chronic GVHD can also appear in patients 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 agents which suppress the immune system, or it could be very severe. It may also last for over a year.

4. **Veno-occlusive disease of the liver.** This is a complication that results from high doses of chemotherapy, or radiation, or both. 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. Although most patients recover completely, veno-occlusive disease can be fatal.
5. **Interstitial pneumonia.** Some patients suffer severe lung problems from either a viral infection called cytomegalovirus (CMV) or a reaction to the chemotherapy given. Although treatments are available, this form of pneumonia can be fatal.
6. **Recurrence of disease.** It is possible that your (your child's) disease may recur even if the transplant is successful. Patients transplanted in relapse have a higher risk of disease recurrence than patients not in relapse at the time of transplant.
7. **Risk of a secondary malignancy.** A second malignancy different from the primary disease may occur following chemotherapy and irradiation.
8. **Central nervous system damage.** Patients with certain kinds of leukemia are at increased risk for central nervous system involvement. Frequently, such patients may have previously received radiation treatments to the head and spine, and/or chemotherapy treatment to the spinal cord fluid. These types of previous treatments may increase the risk of damage to the central nervous system when such patients then receive TBI before the transplant.

Central nervous system damage may include difficulty with thinking and poor ability to concentrate. Subsequent mild learning disability in children may result. There may also be forgetfulness, personality changes, and weakness or paralysis in very unusual cases.
9. **Serious infections.** Full and complete recovery of your (your child's) immune system may take several months following successful marrow engraftment. During this time, there is an increased risk of infections. You (your child) will be prescribed certain medications to reduce the chance of those infections. Preventive treatment is not always effective. If you (your child) have an infection, you (your child) may have to be re-hospitalized after your transplant. Infections may be fatal. Fatal complications of infections include life-threatening pneumonia, liver disease, and/or loss of your (your child's) new bone marrow.
10. **Organ damage.** In addition to the complications listed above, it is possible that the transplant procedure will result in damage to your (your child's) heart, lungs, kidneys and/or

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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.

11. **Genetic Disease Transmission.** There is the potential that certain genetic diseases (such as thalassemia or adrenoleukodystrophy) may be passed through the cord blood transplant. These diseases are very rare. Each cord blood is carefully screened to further reduce the possibility that these genetic diseases are present.

ALTERNATIVE TREATMENTS

The other options potentially available to you are autologous (self) transplantation, a bone marrow transplant from an unrelated donor, a bone marrow transplant from a family member who has a different tissue type (HLA- type), chemotherapy, or no therapy other than supportive care. Each option will be fully explained to you.

You will be informed of the progress of this research study. During the time you are part of it, you will be informed of any new findings which might affect your willingness to continue.

BENEFITS

When compared to unrelated bone marrow transplants, cord blood transplants may have some benefits. These include immediate availability, reduced risk of viral contamination and absence of risk to the cord blood donor. Although it is our hope that this research study will be of benefit to you (your child), and that it will help other patients, we cannot say that it will be directly beneficial to you (your child).

FINANCIAL COST

If you receive a cord blood unit from the COBLT cord blood banks, you will not be responsible for any costs associated with the shipping or testing of the cord blood unit. You will be responsible for the costs of hospitalization, physician's visits, and established diagnostic laboratory tests and the chemotherapy drugs, radiation therapy, and other medicines used in your care. These costs will be the same as for any other bone marrow transplant patient. Further, your (your child's) financial responsibility for this treatment will not be different from that of other patients treated at _____.

If you (your child) are injured as a result of taking part in this research study, emergency care, hospitalization and outpatient care will be made available by the hospital. This will be billed to you as part of your medical expenses. No money will be provided by the hospital as compensation for a research-related injury.

PRIVACY

We request that you permit _____ to use the clinical data included in your treatment records for reporting the results of this program. The results will be reported to the

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National Heart, Lung and Blood Institute, the EMMES Corporation (the Medical Coordinating Center), the Food and Drug Administration, the National Cancer Institute or drug sponsor, and the scientific community. No mention of your (your child's) name or any identifying information will appear in any of these reports. Data will be collected until April 2004 and may continue indefinitely after that date.

Your (your child's) research and hospital records are confidential. Your (your child's) name or any other information which can identify you (your child) will not be used in study reports or publications. It is to be understood, however, that representatives from the Medical Coordinating Center, the National, Heart, Lung and Blood Institute, and the Food and Drug Administration or other authorized agencies may inspect your clinical records without removal of such identifying information.

RIGHT TO REFUSE OR WITHDRAW

The choice to enter or not enter this study is yours. You are in a position to make a decision if you understand what the doctor has explained and what you have read about the research study and possible forms of care. If you decide not to take part, the other choices are available to you (your child) without prejudice. If you (your child) begin the study, you still have the right to withdraw at any time. If you (your child) should withdraw, you (your child) will be offered other available care which suits your (your child's) needs and medical condition. In either case, there will be no penalty or loss of benefits to which you (your child) are entitled.

If you decide to withdraw from this proposed treatment **before** receiving the high doses of drugs, we will continue to offer you (your child) the best available alternative care according to your (your child's) needs and physical condition. Please submit in writing to _____ (*Name of IRB Contact Person*) of your (your child's) decision to withdraw from the study. However, you should understand that if you withdraw from this treatment plan **after** administration of TBI and high doses of chemotherapy, but before infusion of the umbilical cord blood cells, you (your child) might die. The reason is that you (your child) would be left without enough cells in the marrow to produce the white blood cells, platelets and red cells necessary to sustain you (your child).

INSTITUTIONAL REVIEW

_____ (*Name of IRB*) is legally responsible for making sure that research with patients is appropriate and that the patient's rights and welfare are protected. It has reviewed and approved this study.

The physicians in charge of this study are _____ (*Names of Physicians*). If you need more information about this study before you decide to join, or at any other time, you may wish to contact one of them. A non-physician whom you may call for information about the consent process, research patient's rights, or research-related injury is _____ (*Name of Contact Person*) at _____ (*Phone Number*).

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**PATIENT INFORMED CONSENT
FOR CLINICAL RESEARCH**

TITLE: UNRELATED DONOR UMBILICAL CORD BLOOD AS AN ALTERNATE SOURCE OF STEM CELLS FOR TRANSPLANTATION

PURPOSE: The primary purpose of this study is to determine how well cord blood cells from unrelated donors will grow in the new patients' bodies. This study will also determine the side effects that may result from a transplant using unrelated donor cord blood "parent cells".

STATEMENT OF PHYSICIAN OBTAINING INFORMED CONSENT:

I have fully explained this research study to the patient or guardian of patient. In my judgement, and the patient's or guardian's, there was sufficient access to information, including risks and benefits, to make an informed decision.

DATE: _____ **PHYSICIAN'S SIGNATURE:** _____

PHYSICIAN'S NAME: _____

PATIENT'S (OR GUARDIAN'S) STATEMENT:

I have read the description of the clinical research study or have had it translated into a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my/the patient's participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to judge that I want (the patient) to take part in it.

PATIENT NUMBER: _____ **PATIENT'S SIGNATURE:** _____
(Guardian)

PATIENT'S NAME: _____
(Print)

DATE: _____

ASSENT: _____

If the patient is a minor, I have obtained his/her assent to participate in the study to the best of his/her ability to understand.

DATE: _____ **PHYSICIAN'S SIGNATURE:** _____

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A.2 SAMPLE CONSENT FORM FOR PATIENTS WITH NON MALIGNANT DISEASES

Written Summary of Informed Consent

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

You (your child) are being asked to take part in a clinical research study. Clinical research tries to find better ways to diagnose and treat disease. Taking part in any clinical research involves risks and benefits. You need to understand these risks and benefits to make an informed decision about whether or not to join the study. This process is known as informed consent.

This consent form gives detailed information about the research study which your doctor will discuss with you. Once you understand the study, you will be asked to sign this form if you wish to take part. You will have a copy to keep as a record.

The research study you are being asked to join is:

UNRELATED DONOR UMBILICAL CORD BLOOD AS AN ALTERNATE SOURCE OF STEM CELLS FOR TRANSPLANTATION

PURPOSE OF THE RESEARCH STUDY

You (your child) have been asked to participate in a research study to look at the ability of umbilical cord blood cells from an unrelated donor to serve as a source of stem cells for patients undergoing bone marrow replacement. Stem cells can be thought of as “parent cells” of bone marrow. These “parent cells” make new bone marrow which in turn makes red blood cells, white blood cells, and platelets. These cells are absolutely necessary to live. The main purpose of this study is to determine how well cord blood cells from unrelated donors will grow after transplantation into the patient. This study will also determine the side effects that may result from a transplant using unrelated donor cord blood. You (your child) will be one of approximately 350 patients enrolled in this study.

You (your child) have a disease of the bone marrow which is unlikely to be cured with conventional non-transplant treatment. The best results with bone marrow transplantation are obtained when the donor is a relative who has the same tissue type (HLA-type) as the patient. You (your child) do not have such a donor available. This study will investigate whether or not umbilical cord blood may be used instead of marrow cells.

Umbilical cord blood cells are a readily available source of donor stem cells. These cells are obtained by taking blood from the placenta and umbilical cord of the donor at birth and freezing them for future use. This umbilical cord blood has the potential to replace the diseased cells in your (your child)’s bone marrow that normally make white blood cells, red blood cells and platelets.

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To date, approximately 1,000 patients worldwide have been transplanted with umbilical cord blood from unrelated donors. There is no evidence of a difference in long-term bone marrow function between patients who have received umbilical cord blood cells as compared to patients who have received bone marrow. However, the first unrelated cord blood transplant was performed in 1993 and follow-up is limited.

DESCRIPTION OF THE RESEARCH PROCEDURES

You (your child) will undergo an intensive treatment before transplantation of the unrelated donor umbilical cord blood cells. The intensive treatment is designed to kill any abnormal cells in your (your child's) bone marrow. The treatment will also kill all the normal cells in your (your child's) bone marrow.

For patients with Fanconi anemia:

The treatment will include drugs and total body irradiation.

You (your child) will receive cyclophosphamide (Cytosan) and fludarabine for four days intravenously and total body irradiation once.

In addition, you (your child) will receive two drugs to suppress the immune system. The first drug is methylprednisolone. This drug will be given by vein for 5 days before transplant. The second is antithymocyte globulin (ATG). This drug will be given by vein for 5 days before transplant and on day 5, 7, 9, 11, and 13 after transplant. None of these drugs are considered to be experimental. The risks of this intensive treatment are given below.

For patients with severe aplastic anemia:

The treatment will include drugs and total body irradiation.

You (your child) will receive cyclophosphamide (Cytosan) intravenously for two days and 9 doses of total body irradiation.

In addition, you (your child) will receive two drugs to suppress the immune system. The first drug is methylprednisolone. This drug will be given by vein for 3 days before transplant. The second drug is antithymocyte globulin (ATG). This drug will be given by vein for 3 days before transplant. None of these drugs are considered to be experimental. The risks of this intensive treatment are given below.

For patients with a storage disease (e.g. Hurler syndrome, Maroteaux-Lamy syndrome, adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy):

The treatment will include two chemotherapy drugs and two drugs to suppress the immune system.

The chemotherapy drugs you (your child) will receive are busulfan orally for four days, and cyclophosphamide (Cytosan) intravenously for four days.

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In addition, you (your child) will receive two drugs to suppress the immune system. The first drug is methylprednisolone. This drug will be given by vein for 3 days before transplant. The second drug you (your child) will receive is antithymocyte globulin (ATG). You (your child) will receive this drug by vein for 3 days before transplant. None of these drugs are considered to be experimental. The risks of this intensive treatment are given below.

For patients with an immunodeficiency state (e.g. severe combined immune deficiency (SCID), Wiskott-Aldrich syndrome) or other bone marrow failure syndrome:

The treatment will include drugs.

You (your child) will receive busulfan orally for four days, and cyclophosphamide (Cytosan) intravenously for four days.

In addition, you (your child) will receive two drugs to suppress the immune system. The first drug is methylprednisolone. This drug will be given by vein for 3 days before transplant. The second drug is antithymocyte globulin (ATG). This drug will be given by vein for 3 days before transplant. None of these drugs are considered to be experimental. The risks of this intensive treatment are given below.

For patients with a histiocytosis syndrome (e.g. HLH, FEL):

The treatment will include drugs.

You (your child) will receive busulfan orally for four days, etoposide (VP-16) intravenously for three days, and cyclophosphamide (Cytosan) intravenously for four days.

In addition, you (your child) will receive two drugs to suppress the immune system. The first drug is methylprednisolone. This drug will be given by vein for 3 days before transplant. The second drug is antithymocyte globulin (ATG). This drug will be given by vein for 3 days before transplant. None of these drugs are considered to be experimental. The risks of this intensive treatment are given below.

During the period of this intensive treatment and until your immune system shows signs of recovery, you (your child) will be isolated in a protective environment. As part of your (your child's) transplant procedure, you (your child) will have a central venous (Hickman) catheter inserted. This will allow blood to be drawn daily. This will also allow medicine and nutrition to be given daily without having to do several skin punctures. This common procedure is also used for patients receiving marrow transplants.

The umbilical cord blood cells will be given to you (your child) by vein the day following the intensive treatment. These cells will be given back to you (your child) to restore normal bone marrow function. The cord blood will be administered in a small transfusion bag through your (your child's) central venous (Hickman) catheter.

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Following transplantation, you (your child) will receive two medications to decrease the chance of graft versus host disease (GVHD). GVHD is the reaction of the donor cells against your (your child's) body. On the day before the cord blood transplant, you (your child) will receive the drug cyclosporine to suppress your (your child's) immune system. This will be given in your (your child's) catheter until you (your child) is again able to take medications by mouth. Beginning five days after the transplant, you (your child) will also receive more methylprednisolone. This will also be given through your (your child's) catheter until you (your child) are able to take medications by mouth. Both of these drugs will be reduced over a 3-6 month period after transplantation.

You (your child) will receive a drug called granulocyte-colony stimulating factor (G-CSF) starting the day of the transplant. G-CSF will help your (your child's) new "parent cells" grow.

After the transplant, it will be necessary to monitor the ability of cord blood cells to grow in your (your child's) body. Your (your child's) doctors will examine your (your child's) blood (2 teaspoons) and bone marrow (1 teaspoon) on days 30, 60, 90, at 6 months, and yearly after transplantation. This is necessary to make sure that the cord blood cells are growing and making new bone marrow.

Your (your child's) doctors will also evaluate the recovery of your (your child's) immune system. This will require a blood sample (2 teaspoons) on days 30, 60, 90, at months 6, 9, 12, 18, 24, and yearly until your (your child's) immune system is normal. Two-three teaspoonful of additional blood may also be taken and used for HLA typing, chimerism assays and storage for future studies. These studies will not directly benefit you (your child) but will hopefully benefit patients in the future.

The blood will be obtained from your (your child's) catheter until the catheter is removed. Afterwards, it will be collected through your (your child's) vein. Bone marrow samples will be removed from your (your child's) hip bones using a needle and syringe. These procedures may cause brief pain to you (your child).

You (your child) will be followed very closely by the transplant doctors for the first year after transplantation. Your (your child's) doctors will then examine you (your child) at least once a year or more often if there are continuing medical problems.

You (your child) may also be asked to give informed consent for participation in other studies. These studies typically deal with prevention and treatment of transplant problems. You (your child) will only be asked to take part if you (your child) are at risk for developing the particular problem related to the study.

DESCRIPTION OF SIDE EFFECTS AND TREATMENT - RISKS

The side effects associated with transplantation can be uncomfortable and in some cases are potentially dangerous, life-threatening, or fatal. Because this is a research study and the treatments are relatively new, there may be additional side effects which are not known or predictable at this time. Both radiation and drugs may lead to an increased chance of malignancy later in life. **As is true with all medication and treatment, other unexpected side effects may occur.** The known or possible side effects of the pre and post-transplant treatments you may receive as part of this study are listed below:

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The following therapy is used for patients with Fanconi anemia, severe aplastic anemia, and storage disease:

- **Total body irradiation.** Total body irradiation (TBI) may cause transient nausea and vomiting. Anti-vomiting medications can be given as a treatment. TBI may also cause mucositis, an irritation of the lining of the mouth, esophagus, bowel, and rectum. This can lead to mouth pain and ulcers, difficulty swallowing and eating, cramps, and diarrhea. Swelling of the salivary glands may be another problem. Low blood counts, hair loss, and temporary redness of the skin, with later darkening of the skin may also occur.

Late effects of TBI include cataracts. Cataracts are cloudiness in the lens of the eye. They can be surgically corrected. There can be interference with normal growth which can sometimes be corrected with hormone replacement. There can be thyroid and adrenal gland insufficiency. This can be treated with hormone replacement. Permanent sterility may occur. A secondary cancer can also occur. Younger children may be at risk for permanent interference with mental functioning.

The following therapy is used for patients with a storage disease, an immunodeficiency, or a histiocytosis syndrome.

- **Busulfan.** Busulfan may cause vomiting, diarrhea, and seizures. Medication will be given to minimize or prevent some of these side effects. Late effects, which are usually temporary, may include hair loss and increased color of the skin (hyper pigmentation.) Some patients may develop a rash. Some patients may develop mouth sores (mucositis). Some patients may develop abnormal function of the liver or lungs which may be mild, moderate, or potentially fatal if severe.

The following therapy is used for patients with a histiocytosis syndrome:

- **Etoposide (VP-16).** Etoposide (VP-16) has been associated with fever, abnormal depression of all cellular elements of the blood, nerve damage, and elevated liver function tests. More severe toxicities include severe allergic reactions, low blood pressure (hypotension), and secondary leukemia.

The following therapies are used for all patients:

- **Cyclophosphamide.** The high doses of cyclophosphamide may cause low blood counts, hair loss, mucositis and darkening of the skin, and transient nausea and vomiting. Anti-vomiting medications can be given to treat the transient nausea and vomiting.

Less common side effects include water retention which can be treated with medicines; potentially fatal damage to the lungs or liver or weakening of the heart muscle; bloody urine, for which precautions will be taken but which is occasionally very severe.

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- **Antithymocyte globulin (ATG).** Antithymocyte globulin (ATG) has been associated with fever, feeling weak, joint pains, rash, low blood counts, hemolysis, and breakdown of red cells in the blood. More severe toxicities include hives, difficulty breathing, and low blood pressure (hypotension.)
- **Cyclosporine.** The possible side effects of cyclosporine include growth of excessive body hair, reddened gums, increased blood pressure, and liver and kidney damage. In rare instances, central nervous system toxicity with tremor, somnolence (sleepiness), confusion, and seizures may occur. These are reversible after stopping the medication. The amount of cyclosporine in the blood will be monitored to keep these problems to a minimum.
- **Corticosteroids.** Corticosteroids are prednisone (when taken by mouth) and methylprednisolone (when taken by vein). The possible side effects include weight gain and water retention, puffiness of the face, high blood pressure, high blood glucose, bleeding from the stomach and intestines, and personality changes including depression and psychosis. High blood pressure can be treated with medications. High blood glucose can be corrected with insulin.

Although long term corticosteroid administration is not proposed in this study, corticosteroids can be used for treatment of acute and chronic GVHD. Long-term use has been associated with muscle weakness and wasting, cataracts, and suppression of growth in children. It has also been associated with bone thinning. This has sometimes progressed to areas of bone death especially at the knees and hips. In addition, steroids may make you (your child) prone to infections.

- **Granulocyte-Colony Stimulating Factor (G-CSF).** G-CSF will be used to help regrow the new bone marrow. In general, this drug has few serious side effects. Side effects which have been reported include fever, feeling tired, bone pain, and enlargement of the spleen. Additionally, there is a rare risk of allergic reaction to this drug.

In addition to the intensive pre/post-transplant treatment side effects, the following risks may occur:

1. **Bone marrow depression.** Bone marrow depression means decreased blood counts, including red blood cells, white blood cells, and platelets. Until the new cord blood cells begin to grow, you (your child) are 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.
2. **Graft Failure.** The cord blood may fail to “take” or engraft. This may occur in a significant number of patients, depending on the disease for which you (your child) are being transplanted. It is possible that the cord blood will grow, but not work normally. This will

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

result in low blood counts for a long period of time. Graft failure is typically fatal. Should the graft fail, you (your child) will not have access to additional stem cells from the donor.

3. **Graft-versus-host-disease (GVHD).** This condition results from a reaction of the transplanted cord blood cells against your (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 patients. You (your child) will be monitored for this complication and given specific treatment to prevent and treat it. There are two forms: 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, you (your child) may be required to have a skin biopsy and possibly a liver or gut biopsy. The treatment of acute GVHD requires you (your child) to take high doses of corticosteroids. Occasionally, other drugs such as antithymocyte globulin (ATG) are given.

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

4. **Veno-occlusive disease of the liver.** This is a complication that results from high doses of chemotherapy, or radiation, or both. 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. Although most patients recover completely, veno-occlusive disease can be fatal.
5. **Interstitial pneumonia.** Some patients suffer severe lung problems from either a viral infection called cytomegalovirus (CMV) or a reaction to the chemotherapy given. Although treatments are available, this form of pneumonia can be fatal.
6. **Recurrence of disease.** It is possible that your (your child's) disease may recur even if the transplant is successful. Patients transplanted in relapse have a higher risk of disease recurrence than patients not in relapse at the time of transplant.
7. **Risk of a secondary malignancy.** A second malignancy different from the primary disease may occur following chemotherapy and irradiation.
8. **Central nervous system damage.** Patients with certain kinds of leukemia are at increased risk for central nervous system involvement. Frequently, such patients may have previously received radiation treatments to the head and spine, and/or chemotherapy treatment to the spinal cord fluid. These types of previous treatments may increase the risk of damage to the central nervous system when such patients then receive TBI before the transplant.

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Central nervous system damage may include difficulty with thinking and poor ability to concentrate. Subsequent mild learning disability in children may result. There may also be forgetfulness, personality changes, and weakness or paralysis in very unusual cases.

9. **Serious infections.** Full and complete recovery of your (your child's) immune system may take several months following successful marrow engraftment. During this time, there is an increased risk of infections. You (your child) will be prescribed certain medications to reduce the chance of those infections. Preventive treatment is not always effective. If you (your child) have an infection, you (your child) may have to be re-hospitalized after your transplant. Infections may be fatal. Fatal complications of infections include life-threatening pneumonia, liver disease, and/or loss of your (your child's) new bone marrow.
10. **Organ damage.** In addition to the complications listed above, it is possible that the transplant procedure will result in damage to your (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.
11. **Genetic Disease Transmission.** There is the potential that certain genetic diseases (such as thalassemia or adrenoleukodystrophy) may be passed through the cord blood transplant. These diseases are very rare. Each cord blood is carefully screened to further reduce the possibility that these genetic diseases are present.

ALTERNATIVE TREATMENTS

The other options potentially available to you are autologous (self) transplantation, a bone marrow transplant from an unrelated donor, a bone marrow transplant from a family member who has a different tissue type (HLA- type), chemotherapy, or no therapy other than supportive care. Each option will be fully explained to you.

You will be informed of the progress of this research study. During the time you are part of it, you will be informed of any new findings which might affect your willingness to continue.

BENEFITS

When compared to unrelated bone marrow transplants, cord blood transplants may have some benefits. These include immediate availability, reduced risk of viral contamination and absence of risk to the cord blood donor. Although it is our hope that this research study will be of benefit to you (your child), and that it will help other patients, we cannot say that it will be directly beneficial to you (your child).

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FINANCIAL COST

If you receive a cord blood unit from the COBLT cord blood banks, you will not be responsible for any costs associated with the shipping or testing of the cord blood unit. You will be responsible for the costs of hospitalization, physician's visits, and established diagnostic laboratory tests and the chemotherapy drugs, radiation therapy, and other medicines used in your care. These costs will be the same as for any other bone marrow transplant patient. Further, your (your child's) financial responsibility for this treatment will not be different from that of other patients treated at _____.

If you (your child) are injured as a result of taking part in this research study, emergency care, hospitalization and outpatient care will be made available by the hospital. This will be billed to you as part of your medical expenses. No money will be provided by the hospital as compensation for a research-related injury.

PRIVACY

We request that you permit _____ to use the clinical data included in your treatment records for reporting the results of this program. The results will be reported to the National Heart, Lung and Blood Institute, the EMMES Corporation (the Medical Coordinating Center), the Food and Drug Administration, the National Cancer Institute or drug sponsor, and the scientific community. No mention of your (your child's) name or any identifying information will appear in any of these reports. Data will be collected until April 2004 and may continue indefinitely after that date.

Your (your child's) research and hospital records are confidential. Your (your child's) name or any other information which can identify you (your child) will not be used in study reports or publications. It is to be understood, however, that representatives from the Medical Coordinating Center, the National, Heart, Lung and Blood Institute, and the Food and Drug Administration or other authorized agencies may inspect your clinical records without removal of such identifying information.

RIGHT TO REFUSE OR WITHDRAW

The choice to enter or not enter this study is yours. You are in a position to make a decision if you understand what the doctor has explained and what you have read about the research study and possible forms of care. If you decide not to take part, the other choices are available to you (your child) without prejudice. If you (your child) begin the study, you still have the right to withdraw at any time. If you (your child) should withdraw, you (your child) will be offered other available care which suits your (your child's) needs and medical condition. In either case, there will be no penalty or loss of benefits to which you (your child) are entitled.

If you decide to withdraw from this proposed treatment **before** receiving the high doses of drugs, we will continue to offer you (your child) the best available alternative care according to your (your child's) needs and physical condition. **Please submit in writing to _____ (Name of IRB Contact Person) of your (your child's) decision to withdraw from the study.** However,

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

you should understand that if you withdraw from this treatment plan **after** administration of TBI or high doses of chemotherapy, but before infusion of the umbilical cord blood cells, you (your child) might die. The reason is that you (your child) would be left without enough cells in the marrow to produce the white blood cells, platelets and red cells necessary to sustain you (your child).

INSTITUTIONAL REVIEW

_____ (*Name of IRB*) is legally responsible for making sure that research with patients is appropriate and that the patient's rights and welfare are protected. It has reviewed and approved this study.

The physicians in charge of this study are _____ (*Names of Physicians*). If you need more information about this study before you decide to join, or at any other time, you may wish to contact one of them. A non-physician whom you may call for information about the consent process, research patient's rights, or research-related injury is _____ (*Name of Contact Person*) at _____ (*Phone Number*).

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

TITLE: UNRELATED DONOR UMBILICAL CORD BLOOD AS AN ALTERNATE SOURCE OF STEM CELLS FOR TRANSPLANTATION

PURPOSE: The primary purpose of this study is to determine how well cord blood cells from unrelated donors will grow in the new patients' bodies. This study will also determine the side effects that may result from a transplant using unrelated donor cord blood "parent cells".

STATEMENT OF PHYSICIAN OBTAINING INFORMED CONSENT:

I have fully explained this research study to the patient or guardian of patient. In my judgement, and the patient's or guardian's, there was sufficient access to information, including risks and benefits, to make an informed decision.

DATE: _____ **PHYSICIAN'S SIGNATURE:** _____

PHYSICIAN'S NAME: _____

PATIENT'S (OR GUARDIAN'S) STATEMENT:

I have read the description of the clinical research study or have had it translated into a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my/the patient's participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to judge that I want (the patient) to take part in it.

PATIENT NUMBER: _____ **PATIENT'S SIGNATURE:** _____
(Guardian)

PATIENT'S NAME: _____
(Print)

DATE: _____

ASSENT: _____

If the patient is a minor, I have obtained his/her assent to participate in the study to the best of his/her ability to understand.

DATE: _____ **PHYSICIAN'S SIGNATURE:** _____

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

USE OF UMBILICAL CORD AND PLACENTAL BLOOD FROM UNRELATED DONORS AS A SOURCE OF HEMATOPOIETIC STEM CELLS

ASSENT (AGES 8-17 YEARS)

BACKGROUND INFORMATION

After you are treated with chemotherapy and irradiation, your bone marrow no longer produces red blood cells which carry oxygen around the body, white blood cells which fight infection, and platelets which cause your blood to clot when you are cut. Because we all need these cells to live, it is necessary to put back some of the bone marrow's parent cells which will make the bone marrow grow back.

Doctors have learned that these parent cells of the bone marrow can be found in a newborn baby's blood. While we never take blood from a baby, there is some blood left in the umbilical cord and placenta which helps nourish the baby before it is born. We get this blood and save it. It happens that we have found cord blood that matches you. We will give this blood to you after you have completed your chemotherapy and irradiation so that your new bone marrow will grow back.

PROCEDURE

The cord blood will be given through your Hickman catheter either in small syringes or bags. When the blood gets into your body, you may feel sick to your stomach but that will go away quickly. This happens because there are certain drugs in the blood to help keep it safe while it is frozen.

Before the transplant, you will be given a drug called "ATG" and a drug called methylprednisolone. After the transplant, you will also be given a drug called cyclosporine and continued on methylprednisolone. All these drugs can be given through your Hickman.

It will be necessary to check your blood and bone marrow after the transplant to make sure your new bone marrow is growing. Your doctors will do a bone marrow test 21 days, 60 days, and 90 days after the transplant. Blood tests will also be done by taking blood through your Hickman.

RISKS/DISCOMFORTS

It is possible that your new bone marrow will not grow back. If the bone marrow does not grow after the cord blood transplantation, then you will need to get antibiotics since you will not be able to fight infections, and you will need to get blood transfusions since your new bone marrow will not be making new blood cells. There are several possible treatments for this that may help it grow; it may even be necessary to do a second transplant using your own or someone else's bone marrow.

Cyclosporine is a drug that can cause high blood pressure, headaches, and kidney problems. Your doctors will check your blood to make sure that you are getting the right dose of Cyclosporine and that your kidneys are working OK. ATG may cause fevers, rash, joint pain, tiredness, and difficulty breathing. Methylprednisolone may cause nausea, vomiting, sleeplessness, weight gain, and

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

personality changes. G-CSF usually causes few side effects, but may cause fevers, skin rashes, bone aches, or headaches.

QUESTIONS

If you do not want to participate in this study, you don't have to. There are other types of treatment for your disease. If you have any questions about these treatments, please ask the doctors. The doctors want to help you understand what this is all about. If you want to, you can call _____ (*Name of Physician*) at _____ (*phone number*); this is the doctor in charge of this study. The nurses and doctors can help you call.

We want you to understand as much about your treatment with cord blood as possible. If you have asked all your questions and you feel OK about going ahead with this treatment, please sign your name on the first line below. Do not sign your name if you do not want this treatment with cord blood.

Subject's Signature _____
Date

Parent's Signature _____
Date

I have explained fully to the patient the above objective of this study, what is to be expected, and the possible complications.

Counseling Physician's Signature _____
Date

THE PARENTS MUST SIGN A CONSENT FORM.

APPENDIX B

Staging and Grading of Acute GVHD

APPENDIX B

STAGING AND GRADING OF ACUTE GVHD

	Extent of Organ Involvement		
	Skin	Liver	Gut
Stage^x			
1	Rash on < 25% of skin ^a	Bilirubin 2-3 mg/dl ^b	Diarrhea > 500 mL/day ^c (> 280 ml/m ² in children) or persistent nausea ^d
2	Rash on 25-50% of skin	Bilirubin 3.1-6 mg/dl	Diarrhea > 1,000 ml/day (> 555 ml/m ² in children)
3	Rash on > 50% of skin	Bilirubin 6.1-15 mg/dl	Diarrhea > 1,500 ml/day (> 833 ml/m ² in children)
4	Generalized erythroderma with bullous formation	Bilirubin > 15 mg/dl	Severe abdominal pain with or without ileus
Grade^e			
0	None and	None and	None
I	Stage 1-2 and	None and	None
II	Stage 3 and/or	Stage 1 and/or	Stage 1
III	None - Stage 3 with	Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	N/A

^a Use 'Rule of Nines' or burn chart to determine extent of rash.

^b Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

^c Downgrade one stage if an additional cause of diarrhea has been documented.

^d Persistent nausea, vomiting, or anorexia in the absence of other known cause, unless negative histology is present.

^e Criteria for grading given as minimum degree of organ involvement required to confer that grade.

^x Actual symptom/sign collected but stage assignment occurs only if GVHD is indicated as a cause of at least one organ's symptomatology.

APPENDIX C

Chronic GVHD: Clinical and Pathological Manifestations

APPENDIX C

CHRONIC GVHD: CLINICAL AND PATHOLOGICAL MANIFESTATIONS

CGVHD (Chronic Graft-Versus-Host-Disease) is typically a late complication of BMT characterized by a connective-tissue-like syndrome and usually, but not always, occurring greater than 100 days following transplantation. Occasionally, its onset may closely follow acute GVHD (known as progressive presentation of CGVHD). The pathogenesis of CGVHD is believed related to immunological reactivity between host and donor cells, and is probably mediated by allo- and/or auto-reactive T-lymphocytes. Clinically, CGVHD may be manifested by involvement of the following organ systems:

Skin

Skin involvement is usual in CGVHD, occurring in approximately 95% of patients. Manifestations may include an initial, possibly erythematous rash, with or without macules, plaques and/or desquamation. The onset may be acute or insidious. Later, hair follicle atrophy, sclerodermatous changes with skin thickening, progressive epidermal atrophy and fibrosis and hyper- or hypopigmentation may occur. Lichen planus-like lesions may be present. Photoactivation of skin CGVHD may occur. Early histological changes include hyperkeratosis and epidermal hypertrophy. Later changes are epidermal atrophy and dermal fibrosis. Localized lesions may show lichenoid reactions, epidermal atrophy or dense focal fibrosis.

Eye

Symptoms (a sicca syndrome) occur in 80% of patients with CGVHD. Dry, gritty eyes are common and are occasionally associated with photophobia.

Mucosa

The oral mucosa is involved in 80% of cases. Symptoms include oral pain, intolerance of foods and dryness. Signs include diffuse erythema of the oral mucosa, white, lacy mucosal thickening, discrete ulceration and/or lichenoid changes. Oral changes may contribute to inadequate nutrition in some patients. Histological features include labial mucosal atrophy, squamous cell necrosis and mononuclear cell infiltration and minor salivary gland epithelial cytolysis. Vaginal mucosal involvement may lead to vaginal dryness or dyspareunia. Vaginal stenosis has been described.

Gastrointestinal

Anorexia, nausea, vomiting, abdominal pain, and/or weight loss may be manifest with GI involvement. Esophageal involvement may occur in some patients with anorexia and/or dysphagia. An esophageal dysmotility syndrome may also occur. Esophageal biopsy may show mucosal inflammation with desquamation or submucosal fibrosis, though submucosal involvement throughout the GI tract may not be evident on superficial endoscopic mucosal biopsies. 25% of patients overall have significant weight loss and 5% may develop malabsorption with or without chronic diarrhea.

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

Liver

90% of patients have abnormalities of liver function. This is usually a cholestatic pattern, with elevations of bilirubin, alkaline phosphatase, and 5' nucleotidase. Progression to liver failure is rare. Pathological changes include lobular hepatitis with small or absent bile canaliculi.

Joints and soft tissue

Arthritis or systemic lupus erythematosus-like manifestations may occur. Periarticular dermal fibrosis may lead to loss of joint mobility. Contractures may develop as CGVHD progresses. Muscle cramps, usually without myositis, may develop. Polyserositis may occasionally occur.

Pulmonary

Bronchiolitis obliterans with bronchodilator-resistant obstructive lung disease complicates CGVHD in 5% of cases. Diagnosis is established by open lung biopsy, which shows lymphocytic bronchitis, lymphoid interstitial pneumonitis or obliterative bronchiolitis.

Immunological abnormalities and immunodeficiency

Immunological abnormalities include the development of autoantibodies (e.g., FANA, Rheumatoid Factor, positive Coomb's test). Hypogammaglobulinemia, anergy, lymphopenia, functional hypo- or asplenia and immune dysregulation all may lead to increased risk of bacterial, fungal and viral infection.

Other manifestations

Suppression of blood counts may complicate CGVHD. Thrombocytopenia is especially associated with a poor prognosis.

APPENDIX D

Toxicity Grading Scale

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

APPENDIX D

TOXICITY GRADING SCALE

Toxicity Grading

	<u>GRADE I</u>	<u>GRADE II</u>	<u>GRADE III</u>
Cardiac toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder toxicity	Macroscopic hematuria after 2 d from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 d from last chemotherapy dose not caused by infection; or hematuria after 2 d with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary toxicity	Dyspnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF, or decrease of PO ₂ (> 10% from baseline but not requiring mechanical ventilation or > 50% O ₂ on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
Hepatic toxicity	Mild hepatic dysfunction with 2.0 mg% ≤ bilirubin ≤ 6.0 mg%; or weight gain > 2.5% and < 5% from baseline, of noncardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest pre-conditioning	Moderate hepatic dysfunction bilirubin > 6 mg% < 20 mg%, or SGOT increase > 5-fold from pre-conditioning; or clinical ascites or image documented ascites > 100ml; or weight gain > 5% from baseline of noncardiac origin	Severe hepatic dysfunction with bilirubin > 20mg%; or hepatic encephalopathy; or ascites compromising respiratory function

Toxicity Grading

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

CNS toxicity	<u>GRADE I</u>	<u>GRADE II</u>	<u>GRADE III</u>
	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding, or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI toxicity	Watery stools > 500 ml but < 2,000 ml every d not related to infection	Watery stools > 2,000 ml every d not related to infection, or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

Notes: Grade IV regimen-related toxicity is defined as fatal toxicity.

Abbreviations: CXR, chest x-ray; IV, intravenous

Reference: Bearman SI, Appelbaum FR, Bucker CD, Peterson FB, Fisher LD, Clift RA, Thomas ED. (1988). Regimen-related toxicity in patients undergoing bone marrow transplantation. *Journal of Clinical Oncology* **6(10)**:1562-1568.

APPENDIX E

Derivation of a Sequential Test Statistic for Censored Exponential Data

APPENDIX E

**DERIVATION OF A SEQUENTIAL TEST STATISTIC
FOR CENSORED EXPONENTIAL DATA**

Background - The Sequential Probability Ratio Test

Let $f(\cdot, \theta)$ be the density function for a random variable X . According to Neyman and Pearson, the most powerful test of $H_0: \theta = \theta_0$ versus $H_1: \theta = \theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i; \theta_1) / f(x_i; \theta_0)$ is the likelihood ratio, and c_α is determined to have the size α . When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B < 1 < A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N | \theta_j)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $Pr_0(\text{reject } H_0) \leq \alpha$ and $Pr_1(\text{reject } H_1) \leq \beta$, and for which $E_j(N)$ are finite, $j = 0, 1$, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the X_1, X_2, \dots are independent and identically distributed (i.i.d.) with density function $f(x, \theta)$, with monotone likelihood ratio in $T(x)$, then any SPRT for testing θ_0 against $\theta_1 (> \theta_0)$ has a nondecreasing power function.

For the SPRT with error probabilities α and β , the SPRT boundaries are given approximately by $A = (1 - \beta) / \alpha$ and $B = \beta / (1 - \alpha)$. The operating characteristics of the SPRT are given by $O(\theta; \alpha, \beta, \theta_0, \theta_1) = (A^{h(\theta)} - 1) / (A^{h(\theta)} - B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to $\int (f(x; \theta_1) / f(x; \theta_0))^{h(\theta)} f(x; \theta) dx = 1$. The average sample number for an arbitrary θ is given by $E(N; \theta) = [\{1 - O(\theta)\} \log A + O(\theta) \log B] / E(Z; \theta)$. The sample size distribution is very highly skewed, $Var(N) \sim [E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 , and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Uncensored Exponential Survival Times

We wish to construct a sequential test for the composite null hypothesis that survival at six months is greater or equal to 60% versus the composite alternative hypothesis that it is less than or equal to 60%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 5%, and that the test provide 80% power to reject the null hypothesis under a specified alternative that the true survival rate is 40%. A maximum sample size of 75 patients will be permitted.

Let us assume that the survival times, T_1, T_2, \dots, T_n , are completely observed (uncensored) and are i.i.d. with exponential density function $f(T, \theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, six month survival of 60% translates into a mean survival of 0.979 years ($\theta_0 = 1.021$) and 40% translates into a mean survival of 0.546 years ($\theta_1 = 1.832$).

APPENDICES - CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, $H_0:\theta=\theta_0=1.021$ versus $H_1:\theta=\theta_1=1.832$. However, since the log-likelihood ratio for the exponential, $\log\prod_i^n f(x_i;\theta_1)-\log\prod_i^n f(x_i;\theta_0)=n(\log(\theta_1)-\log(\theta_0))-(\theta_1-\theta_0)\sum_i^n T_i$, is a monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ . Thus the SPRT is a one-sided level .05 test of a composite null ($H_0:\theta\geq\theta_0=1.021$) versus a composite alternative ($H_0:\theta\leq\theta_0=1.021$), with power of $1-\beta=0.80$ at the selected alternative $\theta=\theta_1=1.832$.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\log\theta_0-\log\theta_1)/(\theta_0-\theta_1)=0.721$, and intercepts $\log A/(\theta_0-\theta_1)=-3.42$ and $\log B/(\theta_0-\theta_1)=1.92$, for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the cumulative sum of failure times $\sum_i^n T_i$ is recomputed, and plotted against the current sample size n . When this graph crosses the lower boundary, the null hypothesis is rejected.

The maximum sample size of 75 patients requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 75 patients, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 75 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT Test for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. We believe that the hazard is reasonably constant over the first six months on trial, and is likely to decrease substantially thereafter. Furthermore, it is not practical to conduct a clinical study by putting each individual on trial, and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from entry to failure, or to the six month time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times T_1, T_2, \dots, T_n with censored failure times X_1, X_2, \dots, X_n , and the current sample size n with the number of observed failures d .

Now we relax the second assumption, and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 75 patients to the study, and that the final analysis takes place six months after the last patient is entered. Putting this all together, we propose a modified truncated SPRT, where at any interim time point, s , ranging from 0 to 3.5 years, the sum of observed time on study, $\sum_i^n X_i(s)$, is plotted against the number of observed failures, $d(s)$.

A further modification made to the SPRT was to only use the lower boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 180 day survival.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

The modified SPRT for censored exponential survival times targeted a drop in survival from 60% to 40%, rather than from 60% to 45%, as was used for the derivation of the uncensored test. Requiring type I and type II error rates of 0.05 and 0.20, and solving for the parameters of the SPRT, we obtain $A = 16$, and $B = 0.21$. Since only the lower boundary is used for monitoring, the continuation region of the test is bounded below by a line with slope of 0.72 and intercept of -3.4. Under the further assumption of uniform accrual over a three year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study.

Table E.1 Operating Characteristics of Sequential Testing Procedure from a Simulation Study with 100,000 Replications

True 6 Month Survival	60%	50%	40%	30%
Probability Reject Null	0.04	0.38	0.91	1.00
Mean Month Stopped	41.1	33.8	19.3	11.3
Mean # Deaths in 6 Mo.	29.3	30.5	21.1	13.4
Mean # Patients Enrolled	73.5	62.6	39.2	23.7

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true survival rate at six months was 60%, the test crossed the lower boundary in 3759 of 100,000 replications, for an estimated type I error rate of 0.038. When the true survival rate at six months was 40%, the test failed to cross the lower boundary (either crossed the upper boundary or remained in the continuation region) in 9214 of 100,000 replications, for an estimated type II error rate of 0.09. The test is almost certain (100%) to reject the null hypothesis when the true survival rate at six months is 30%.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at six months, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the six month failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first six month period is high, the exponential test will reject faster than the binomial test, but have not conducted simulation studies to demonstrate this.