Informed Consent to Participate in Research

Principal Investigator Contact Information
(Insert contact information for PI at your site)

Study Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Additional support is provided by GlaxoSmithKline Corporation, which makes one of the drugs (Bexxar) used in this study. GlaxoSmithKline will provide this drug free of charge. However, this company did not plan or design this clinical trial and will not have a part in analyzing the results of this study.

Introduction
This is a clinical trial, which is a research study to answer specific medical questions. The information from this study will help future patients. The Study doctor (the person in charge of the research) will explain the clinical trial to you. Clinical trials include only people who choose to join the study.

Please take your time to decide if you want to join this study. Some people find it helpful to talk about the study with their family and friends before they make a decision. It may also be useful to talk with your doctor and other people on your health care team about the study. If you have questions or want to know more about the study, you can ask them for more information.

You are being asked to take part in this study because you have Non-Hodgkin's Lymphoma (NHL) which has either not fully responded to treatment or has returned after an initial response. In this situation, many patients with NHL are treated with autologous peripheral blood stem cell transplantation. An autologous peripheral blood stem cell transplant is when your own stem cells are collected from your blood, frozen, and then given back to you after you receive chemotherapy, also referred to as conditioning therapy. There are a number of ways that an autologous stem cell transplant can be done.

Why is this study being done?
An important part of the transplant procedure is the high dose chemotherapy (called the conditioning regimen) given to try to get rid of all lymphoma cells. Although many people are cured of their NHL with this therapy, the lymphoma comes back in a large minority. This study compares two different conditioning regimens, one using the drugs Rituxan and BEAM (a mixture of the chemotherapy drugs BCNU, Etoposide, Ara-C, and Melphalan) and the other using the drugs Bexxar and BEAM, to find out which is better at curing lymphoma or if they are the same. In this study, you will get either the Rituxan/BEAM conditioning regimen or the Bexxar/BEAM conditioning regimen. You will not get both. Results of this trial will help doctors make better treatment decisions for future patients.

How many people will take part in the study?
Two hundred twenty-four patients will take part in this study. Half of the patients (112 patients) will receive the Rituxan/ BEAM pre-transplant conditioning and half (112 patients) will receive the Bexxar/ BEAM pre-transplant conditioning.

What will happen if I take part in this research study?
Before you begin the study **--** You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. The tests include:

- Medical history
- Physical examination, including height and weight
- Blood and urine tests
- EKG
- Heart function tests
- Pulmonary (lung) function tests
- Thyroid function test
- Tests to evaluate your lymphoma including scans and a bone marrow biopsy
- A blood pregnancy test if you are a woman able to have children; if you are pregnant, you will not be able to take part in this study.

During the study *(you can refer to the Study Chart later in this consent as you read this)* **–**

Randomization

All the exams, tests, and procedures described to this point are part of regular cancer care and may be done even if you do not join the study. However, if you were receiving regular cancer care, your doctor would choose the next treatment for you. As part of this study, we want to compare regular cancer care to an experimental treatment. To do this, you will be **randomized**

into one of the two conditioning regimen study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. You have a 50/50 chance of receiving each therapy. Neither you nor your doctor can choose the group you will be in.

Conditioning Regimen

The conditioning regimen is used to kill the lymphoma cells in your body.

- If you are in Group 1, you will receive the Rituxan/BEAM pre-transplant conditioning regimen. You will receive Rituxan on the 19th and 12th days before your transplant by intravenous infusion (through your vein). You will receive BEAM chemotherapy starting 6 days before your transplant. You will then receive the autologous cells that were collected and frozen during mobilization (this day that you receive your cells is referred to as Day 0). BEAM is a very common combination of chemotherapy drugs that has been widely used in transplants for NHL. Rituxan is an antibody against lymphoma cells that is commonly used both to treat lymphoma without a transplant and as part of transplant care.
- If you are in Group 2, you will receive the Bexxar/BEAM pre-transplant conditioning regimen. You will receive Bexxar on the 19th and 12th days before your transplant by intravenous infusion**.** You will receive BEAM chemotherapy starting 6 days before your transplant. On Day 0, you will receive the autologous cells that were collected and frozen after during mobilization. Bexxar is a new drug that was FDA approved for treatment of certain types of lymphoma but has not been used extensively in treatment of diffuse large B cell lymphoma or in transplants for NHL. The use of Bexxar is the investigational part of this study.

Reinfusion of Stem Cells (Transplantation)

After the conditioning regimen, the stem cells that were previously collected and frozen will be thawed and reinfused into you through your catheter. The cells will travel to your bone marrow where they'll begin making healthy, new blood cells. This step is necessary because the high dosages of chemotherapy given to you during the conditioning regimen will not only destroy lymphoma cells, but healthy cells in your bone marrow as well. Until the new stem cells begin producing healthy blood cells, you will be at an increased risk of excessive bleeding or developing an infection.

Description of Study Drugs

Rituxan (Rituximab) - Rituxan is a drug that can recognize lymphoma cells and either kill them and/or cause other immune cells in the body to kill them.

Bexxar - Bexxar is also a drug that recognizes lymphoma cells but, in addition, has a radioactive compound attached to it. When Bexxar attaches to lymphoma cells, the cells are killed by the radiation released by the radioactive compound. Bexxar is given to patients by physicians and

staff with experience in handling radioactive compounds, usually in the Nuclear Medicine Department of a hospital. Most patients receive this treatment as an outpatient. However, because the radioactivity of Bexxar lasts for several days, you will have to follow some precautions for several days to avoid exposing others to radiation. You will receive instruction on these precautions before treatment but they include sleeping in a separate bed and avoiding close, prolonged contact with children and pregnant women. The risk to others is very low.

BEAM- BEAM is a mixture of several chemotherapy drugs that interfere with the growth of cancer cells and are widely used to treat NHL:

BCNU (also called carmustine)

Etoposide (also called VP-16)

Ara-C (also called cytarabine)

Melphalan

When you are finished taking these drugs and have received your transplant, you will be watched closely. For this study, you will have the following tests at least twice per week for the first 4 weeks and then again at 8 weeks, 100 days, six months, one year and two years after transplantation:

- Medical history
- Physical examination
- Blood and urine tests

In addition to these tests, you will have blood drawn to test how well your immune system is working at 100 days, six months, one year, and two years after your transplant. Tests of your thyroid gland and your lung function will be done at one year and two years after your transplant. Your doctor may also require you to have tests of your thyroid gland for more than two years after your transplant.

Tests and exams to look at the status of your lymphoma will be done 100 days, 6 months, 1 year and 2 years after your transplant. These will include scans and bone marrow biopsies.

All of these exams, tests or procedures are part of regular medical care after a transplant and may be done even if you do not join the study. The schedule for testing is only for tests required for the study. Some of these tests will be done more frequently than described here if your doctor thinks it is necessary for your medical care.

How long will I be on this study?

After your transplant, the study doctor will ask you to visit the office for follow-up exams for two years to receive the study tests and procedures described above. Your doctor will also collect information on how you are doing for up to five years after your transplant.

Follow up for your transplant will last as long as you require care. However, we would like to keep track of your medical condition for the rest of your life by contacting you and the doctor

providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study and transplantation in general. Many transplant centers include this type of long-term follow-up as part of their regular medical care. It is not necessary for you to agree to follow-up for longer than 5 years to participate in this study.

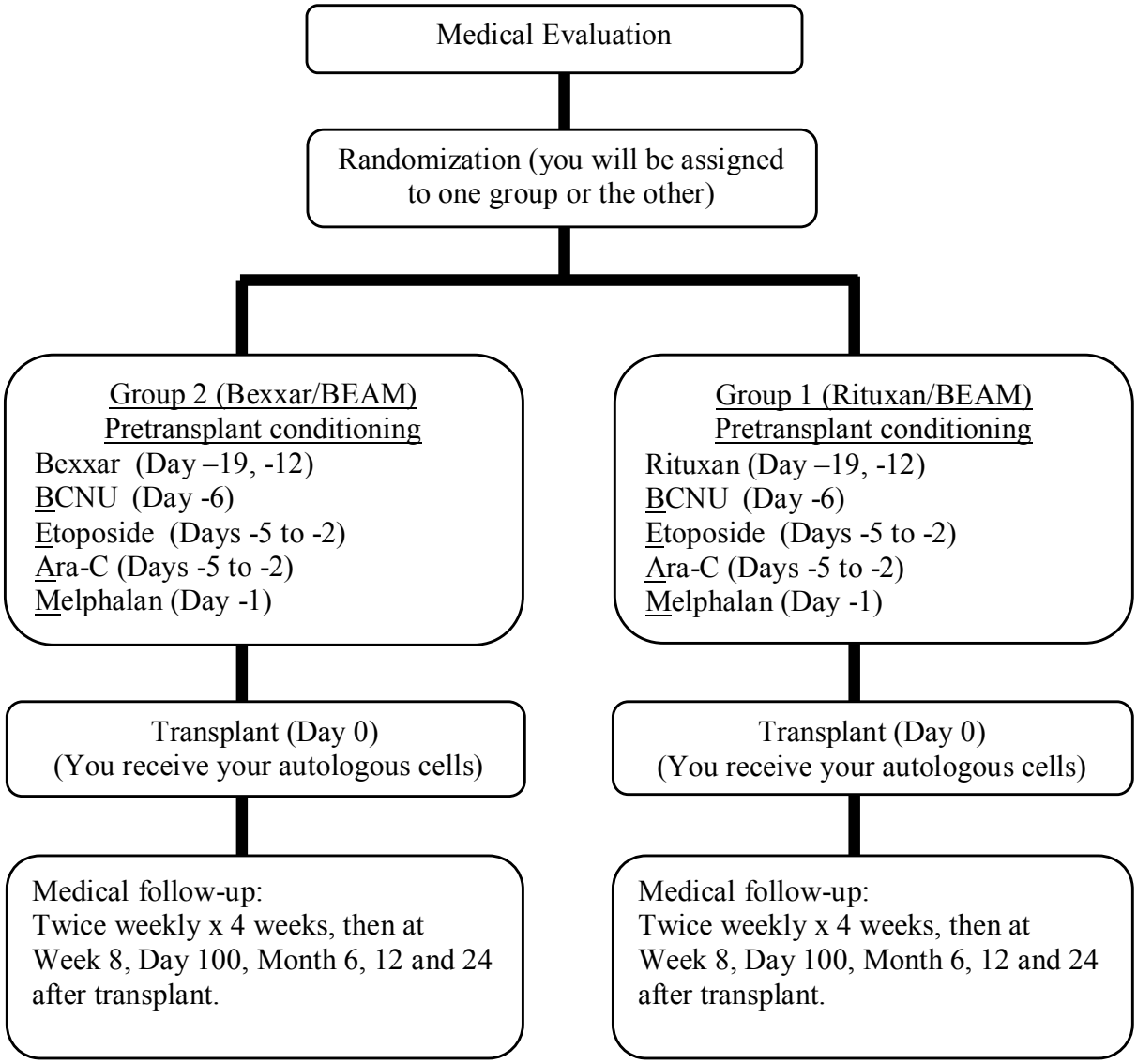
Can I stop being in the study?
Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the medications can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Can the Study Doctor withdraw me from the study?
You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- You need a medical treatment not allowed in this study.
- The study doctor decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the dose of study drug you are taking is found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).

STUDY CHART -


Medical Evaluation
Randomization (you will be assigned to one group or the other)
Group 2 (Bexxar/BEAM)
Pretransplant conditioning
Bexxar (Day –19, -12)
BCNU (Day -6)
Etoposide (Days -5 to -2)
Ara-C (Days -5 to -2)
Melphalan (Day -1)
Group 1 (Rituxan/BEAM)
Pretransplant conditioning
Rituxan (Day –19, -12)
BCNU (Day -6)
Etoposide (Days -5 to -2)
Ara-C (Days -5 to -2)
Melphalan (Day -1)
Transplant (Day 0)
(You receive your autologous cells)
Transplant (Day 0)
(You receive your autologous cells)
Medical follow-up:
Twice weekly x 4 weeks, then at Week 8, Day 100, Month 6, 12 and 24 after transplant.
Medical follow-up:
Twice weekly x 4 weeks, then at Week 8, Day 100, Month 6, 12 and 24 after transplant.

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. Many of these side effects are possible regardless of the type of autologous transplant you receive. It is possible that some of these side effects are increased by the drugs used in this study or that these drugs will have new side effects that we don't know about now.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Potential Side Effects

Rituxan		
Likely	**Less Likely**	**Rare but Serious**
• Shaking chills • Fever • Itching	• Low blood pressure • Shortness of breath • Rash • Nausea/vomiting • Diarrhea • Headache • Throat irritation • Night sweats • High blood sugar level	• Low blood counts • Tiredness • Pain from areas of lymphoma • Cardiac arrhythmia • Chest pain • Renal failure • Angioedema • Angina • Progressive Multifocal Leukoencephalopathy (PML)
GCSF (Filgrastim)		
Likely	**Less Likely**	**Rare but Serious**
• Muscle pain • Bone pain	• Fluid retention • Fluid around the heart • Pain and swelling at the injection site	• Allergic reactions • Spleen swelling • Spleen rupture • Difficulty breathing

Bexxar		
Likely	**Less Likely**	**Rare but Serious**
• Low blood counts	• Allergic reaction • Nausea/vomiting • Abdominal pain • Diarrhea • Low thyroid hormone • Constipation • Anorexia • High blood pressure • Headache • Itching • Sweating • Skin rash • Cough	• Fever, shaking chills • Low blood pressure • Difficulty breathing • Abnormal bone marrow • Second cancers, including MDS and leukemia • Human Anti-Mouse Antibodies
BEAM		
Likely	**Less Likely**	**Rare but Serious**
• Low blood counts • Nausea/vomiting • Mouth sores • Sores in esophagus • Abdominal pain/diarrhea • Difficulty eating • Hair loss • Fatigue	• Liver problems • Lung problems • Low blood pressure • High levels of uric acid • Skin rash • Chills	• Liver failure • Severe lung problems • Severe allergic reactions • Second cancers, including MDS and leukemia • Life-threatening infection • Disease of the peripheral nervous system • Sterility

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

Hepatitis B Reactivation: In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as Rituxan. This could lead to liver failure or even death. The risk of hepatitis B virus flaring up may continue for several months after you stop taking Rituxan. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking Rituxan or after stopping treatment, you should tell your study doctor immediately. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Progressive Multifocal Leukoencephalopathy (PML): In the past, the FDA has reported a very rare case of two deaths that were reported after patients had been treated with Rituxan for systemic lupus erythematosus (SLE). These deaths have been caused by a viral infection of the brain called progressive multifocal leukoencephalopathy (PML). In rare cases, you may encounter problems with speech or movement, or in very rare cases death. Please notify your doctor immediately if you have any new or worsening memory loss, trouble thinking, difficulty walking, or changes in vision.

Potential Allergic Reactions to Murine Proteins: Bexxar is a mouse (murine) protein antibody. You should notify your physician if you know that you have received a product containing mouse antibodies. Some patients that have previously been exposed to products containing mouse antibodies may develop their own antibodies against mouse proteins. This may happen to you after you receive Bexxar. These are called human anti-mouse antibodies or HAMA. The presence of HAMA may possibly make a person more likely to develop an allergic reaction to mouse proteins, but this is not proven. Unfortunately, there is no well-accepted test for measuring HAMA and it is not known whether the presence of HAMA would let us know if you would have an allergic reaction to mouse proteins. Therefore, we will not be testing for HAMA in this study. In the event that you do have an allergic reaction, epinephrine (a drug used for cardiac arrest) and antihistamines (drugs used for allergic reactions) will be available at your bedside during the administration of Bexxar.

This study is designed to help persons who are suffering from Non-Hodgkin's Lymphoma (NHL). A risk remains, however, that neither treatment arm will be successful in curing or improving your illness.

After you have recovered from your stem cell transplantation, your doctor may consider additional radiation to areas where you have had lymphoma. If so, your doctor will review with you the rationale and potential side effects at that time.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. This research study is comparing two pre-transplant conditioning regimens. At this time doctors do not know if one conditioning regimen has better results than the other, or if they both have the same results. We do know that the information from this study will help doctors learn more about transplantation for NHL. This information could help future patients with NHL.

What other choices do I have if I do not take part in the study?
Your other choices may include:

- Treatment with other drugs or a combination of drugs without a transplant.
- An autologous stem cell transplant that is not part of the study or another type of transplant.
- No therapy directed against your lymphoma at this time.

Talk to your doctor about your treatment choices before you decide if you will take part in this study.

What are the costs of taking part in this study?
You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The company that manufactures Bexxar will provide this drug at no cost. All other costs of your care including the chemotherapy drugs and costs associated with administration of them will need to be paid by you and/or your health plan/insurance company. All of the medical tests, evaluations and procedures in this study are considered part of standard medical care.

The companies that make the drugs used in this study did not plan or design this clinical trial. They will also not have a part in analyzing the results of this study.

You will not be paid for taking part in this study.

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

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will my medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research, organizations involved in research on blood and marrow transplantation and in the coordination of this study
- The EMMES Corporation, a research organization that is helping to coordinate this study
- Members of the Blood and Marrow Transplant Clinical Trials Network, which is conducting this study
- The National Heart Lung and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Southwest Oncology group (SWOG), clinical trials cooperative group

Information about the results of this study will also be provided to the GlaxoSmithKline Company (which makes Bexxar) but without any identifying information.

HIPAA[1] authorization to use and disclose individual health information for research purposes

a. - Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *Phase III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-cell Non-Hodgkin's Lymphoma*.

b. - Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results).

c. - Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(list hospitals, clinics or providers from which health care information can be requested)

_____

_____

_____

d. - Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Members of the BMT CTN Data and Coordinating Center and 0401 Protocol Team
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Southwest Oncology group (SWOG), clinical trials cooperative group
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

1 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- Other:

_____

_____

_____

e. - Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. - Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. - Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. - This authorization does not have an expiration date.

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About Using Blood for Research

Please note: This section of the informed consent form is about future research studies that will be done using blood samples from people who are taking part in the main study described above. You may give blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to giving blood samples for future research studies. You can say "yes" or "no" to giving blood samples for future research studies. Please mark your choice at the end of this section.

We would like to have a blood sample for future research. If you agree, 1 tablespoon (10 mL) of blood will be obtained at the time other blood samples are drawn at the beginning of the study and will be kept and may be used in research to learn more about cancer and other diseases. When the sample is given to investigators for research, no information about name, address, phone number of other information that will let the researcher know who you are will be provided.

The sample collected for research purposes will be sent to the National Heart, Lung, and Blood Institute (NHLBI) sample repository in Maryland. The sample will be labeled with unique codes that do not contain information that could identify you. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the repository where your sample is being stored does not have a link to this code. Your sample will be stored at this repository until the entire sample has been used for the research tests or until the end of the study. Any research performed on this sample must first be approved by an advisory panel at the NHLBI.

The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About: The choice to let us have a blood sample for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

Benefits: The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks: The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice: Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

- ❑ Yes, I agree to have blood drawn for future research.
- ❑ No, I do not agree to have blood drawn for future research.

_____ _____
Signature *Date*

****

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____*[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Witness _____

Date_____

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____
Signature of person conducting informed consent

_____
Date