Medical College of Wisconsin and Froedtert Hospital
CONSENT TO PARTICIPATE IN RESEARCH

Name of Study Subject: _____

RANDOMIZED CONTROLLED PILOT STUDY USING PROPRANOLOL TO DECREASE GENE EXPRESSION OF STRESS-MEDIATED BETA-ADRENERGIC PATHWAYS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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You are invited to take part in this research study. This form tells you why this research study is being done, what will happen in the research study, possible risks and benefits to you, your choices, and other important information. If there is anything that you do not understand, please ask questions. Then you can decide if you want to join this study or not.

A1. INTRODUCTION – WHY ARE WE ASKING YOU ABOUT THIS STUDY?

You are being invited to participate in this research study of a common medication, propranolol, because you have multiple myeloma and are planning on receiving an autologous hematopoietic stem cell transplant (more commonly, a transplant of stem cells from your peripheral blood). This study is looking at how a common medication, propranolol, might improve your body's response to the transplant and your cancer outcome.

A total of about 40 people are expected to participate in this study all at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the study is Jennifer Knight, MD in the Department of Psychiatry. A study team works with Dr. Knight. You can ask who these people are.

The National Institutes of Health, a government agency, is funding this study.

A2. DO I HAVE TO BE IN THIS STUDY?

You can decide whether to take part in this study or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this study, you do not have to stay in it. You may stop at any time.

A research study is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the study procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS RESEARCH STUDY BEING DONE?

Patients who have multiple myeloma and undergo autologous transplants may be at risk for cancer relapse. This study is looking at whether people going through a transplant can and will take propranolol, a common medication that may improve cancer outcomes. This study looks at effects of the propranolol on your genes. This study also looks at how propranolol affects your body's response to the stress of transplant as well as cancer outcomes. Finally, you will be asked about any feelings of depression and anxiety that you might have during transplant, as this may contribute to the way propranolol affects your cancer.

B1. WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

Baseline Visits

You will have medical tests and procedures to help the study doctor decide if you can be in the study. This is called "Screening," which will start at your first visit to the study site. Whether you can be in the study will depend on the results of your Screening tests, disease assessments, and the judgment of the study doctor. The study doctor and/or the study staff will discuss this with you. Screening for this study includes the tests and procedures below:

- Informed consent form signed
- Your demographic, socioeconomic and medical information will be collected
- You will be asked to complete a questionnaire about anxiety, depression and socioeconomic status. This will take approximately 15 minutes to complete.
- You will have blood taken for research samples.
- If you are able to become pregnant you will have a pregnancy test
- A measurement of your heart rate and blood pressure will be taken
- We will see how you are doing
- We will look at your medical status

If you meet the requirements to enter the study and agree to participate, you can begin the study.

Study Conduct

Because no one knows if treatment with or without propranolol is best, you will be "randomized" into one of the two study groups. One group will receive propranolol. The other group (control group) will not receive propranolol. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group. Neither you nor the study doctor can choose what group you will be in.

Propranolol group:

If you are assigned to the group taking propranolol, 1 week (7 days) before your scheduled transplant you will begin taking propranolol. You will take 20 mg by mouth two times a day for about one week. You will be watched closely by your study doctor to see how you are doing. After approximately one week if you are not having any serious side effects your study doctor will increase your dose of propranolol to 40 mg by mouth two times a day. If you tolerate, propranolol you will continue to take it for 4 weeks after your transplant at which time the drug will be stopped or weaned.

Control group:

If you are assigned to the control group you will have your transplant as scheduled per your clinical care. You will have the same blood draws and questionnaires as described below for both groups.

No matter which group you are in you will have many of the same study visits, tests and procedures, but only patients in the propranolol group will receive the study drug.

Summary of Study Procedures:

Day -2 prior to your transplant (Both Groups)

No matter which group you are in, you will have a visit 2 days before your transplant. At these visits you will have the following tests and procedures:

- You will be asked to bring your pill bottle to these visits (Propranolol Group Only)
- You will be asked to complete questionnaires about anxiety and depression. This will take approximately 15 minutes to complete.
- You will be asked how you are doing
- You will have mandatory blood taken for research samples on day -2 (2 days before your transplant) only (described below).
- A measurement of your heart rate and blood pressure will be taken

Days 7, 14, 21, 28 after your transplant

- You will be asked to bring your pill bottle to these visits (Propranolol Group Only)
- You will be asked to complete a questionnaire about anxiety and depression. This will take approximately 15 minutes to complete.
- The study team will collect information from your medical record about your transplant
- You will be asked how you are doing
- You will have mandatory blood taken for research samples on day 28 after your transplant only (described below).
- A measurement of your heart rate and blood pressure will be taken

If you are in the control group day 28 will be your last study visit.

Days 35 and 42 after your transplant (Propranolol Group Only)

- You will be asked how you are doing

At your next clinic appointment after stopping Propranolol (Propranolol Group Only)

- You will be asked to bring your pill bottle and return any unused study medication
- A measurement of your heart rate and blood pressure will be taken

Day 100 after your transplant

- We will check your medical record to see how your disease is responding to the transplant

Propranolol group weaning

When you are done with the study treatment phase (28 days after your transplant) or if you have side effects that require you to stop taking your study drug, propranolol, you will begin weaning. If you are currently taking the 40 mg dose twice daily, you will be weaned to the 20 mg dose twice daily for one week before stopping completely. If you are on the 20 mg dose twice daily you will be stopped completely.

Research Samples

As part of this study, 3 tubes of blood (approximately 2.5 mL each) will be taken for research. These will occur: approximately 1-2 week prior to transplant, two days prior to your transplant, and 4 weeks after transplant. These samples will be used to see if the propranolol is causing a change in protein production.

Genetic testing is done on blood and other specimens. In this study, we will do genetic testing on your blood. Genetic testing will be done to determine whether propranolol

impacts your genes and how your body responds to the stress of your hematopoietic stem cell transplant. This genetic study is for research only. The purpose is not to discover information that could be used to change your medical care, make or change your diagnosis, or advise you on your risk of diseases.

Only your study number will be included with your blood sample. The study team will have the code that links your study number to your blood sample. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you. It is against federal law (GINA) for health insurance companies to deny health insurance, or large employers to deny jobs, based on your genetic information. But the same law does not protect your ability to get disability, life, or long term care insurance. If you have questions, you can talk to the study doctor about whether this could apply to you.

My decision about the genetic study

Initial either 1 or 2:

1.____I do NOT want genetic testing done on my blood in this study. This means that I cannot participate in the study.
Stop here and speak to Dr. Knight. Do not sign this form.

2.____I agree to have genetic testing done on my blood in this study.

B2. HOW LONG WILL I BE IN THE STUDY?

You will be in this research study for approximately 17 weeks.

B3. CAN I STOP BEING IN THE STUDY?

You are free to withdraw from the study at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the study doctor.

⇒ The doctor can tell you about the effects of stopping, and you and the doctor can talk about what follow-up care would help you the most.
⇒ You will be asked to come back for one more visit to check your health.
⇒ You will be asked to return your research drug containers.

The study doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the study rules.
- The whole study is stopped.

If this happens, the study doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE STUDY?

There are risks to taking part in any research study. There is a risk that you may get an intervention that does not help your condition or may make it worse. There also may be

problems (side effects) we do not know about yet, from the drug itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the study for problems (side effects). **You need to tell the study doctor or a member of the study team immediately if you experience any problems, side effects, or changes in your health.** If you have any problems, call your transplant physician. In an emergency, call 911.

C2. RISKS OF PROPRANOLOL

The research drug itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away. Many go away soon after you stop taking the drug. Drugs can affect individuals in different ways. Complications of some of the side effects below may lead to life-threatening events such as slow or irregular heart rate and allergic reactions.

- Rare
  - Dizziness or passing out
  - Hard stools (constipation)
  - Loose stools (diarrhea)
  - Upset stomach or throwing up
  - Feeling sleepy
  - Feeling tired or weak
  - Not able to sleep

- Rare but serious adverse events that have been reported
  - Chest pain that is new or worse
  - Change in thinking clearly and with logic
  - Hallucinations
  - Memory problems or loss
  - Mood changes
  - A burning, numbness, or tingling feeling that is not normal
  - Change in eyesight
  - Shortness of breath, a big weight gain, swelling in the arms or legs
  - Any bruising or bleeding
  - Slow heartbeat
  - A heartbeat that does not feel normal
  - Feeling cold
  - Low blood sugar, signs may include dizziness, headache, feeling sleepy, feeling weak, shaking, a fast heartbeat, confusion, hunger, or sweating.
  - A very bad skin reaction (Stevens-Johnson syndrome/toxic epidermal necrolysis) may happen. It can cause very bad health problems that may not go away, and sometimes death. Get medical help right away if you have signs like red, swollen, blistered

or peeling skin (with or without fever), red or irritated eyes, or sores in your mouth, throat, nose, or eyes.

- In some cases if you stop taking propranolol all of a sudden you may develop chest pain that is worse and in some cases a heart attack may occur. This risk may be greater if you have certain types of heart disease. To avoid side effects, do not stop taking propranolol all of a sudden, you want to slowly stop this drug as ordered by your doctor. Call your doctor right away if you have new or worse chest pain or if other heart problems occur.

- Allergic Reactions
  - Allergic reaction, such as rash; hives; itching; red, swollen, blistered or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue or throat

In some cases if you stop taking propranolol all of a sudden you may develop chest pain that is worse and in some cases a heart attack may occur. This risk may be greater if you have certain types of heart disease. To avoid side effects, do not stop taking propranolol all of a sudden, you want to slowly stop this drug as ordered by your doctor. Call your doctor right away if you have new or worse chest pain or if other heart problems occur.

C3. OTHER RISKS OF THIS RESEARCH STUDY

Blood Samples:
The tests done at each visit are standard medical tests. The samples obtained for research purposes will be collected at the same time that you are having routine blood collections to monitor the status of the transplant and your disease. There are aspects often associated with having blood samples taken that can be viewed as unpleasant. These include may include fainting, pain and/or bruising. Rarely, there may be a small blood clot or infection at the site of the needle puncture. The blood pressure cuff may also cause discomfort or bruising to the upper arm.

Confidentiality:
Another risk may be loss of confidentiality. Every effort will be made to keep your study records confidential but we cannot guarantee it. Depending on the kind of information being collected, if your study information were accidentally seen, it might be used in a way that could make you uncomfortable or affect your ability to get insurance. If you have questions, you can talk to the study director about whether this could apply to you.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant

The drug in this study might affect a baby, before or after the baby is born. We do not know if the drug causes harm to a baby, so we do not want anyone who might be pregnant to enter the study. You should not become pregnant or nurse a baby while in this study. You must tell the study doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the study.

Risks of fathering a child

You should not father a baby while taking part in this study because it is unknown if the drug in this study could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the study doctor right away if you think your partner is pregnant.

Birth control methods for all subjects

Check with the study doctor about the birth control methods needed for this study and how long to use them. Some methods might not be good enough for this study. If you are having sex that could lead to pregnancy, you should use birth control while you are in this study.
This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms (“double barrier”)
- Limiting sexual activity to a male partner who has had a vasectomy

You should continue using birth control for 30 days after stopping the Propranolol.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

This study may or may not help you, but we hope the information from this study will help us develop better treatments for controlling cancer progression.

D1. ARE THERE ANY COSTS TO BEING IN THE STUDY?

The medical care you receive in this study is considered routine care for your condition and would be recommended whether you join the study or not. Costs for routine care will be billed to you or your insurance carrier. Activities / costs that are part of the study will not be billed to you or your insurance company. These are the questionnaires, research only blood draws, processing and shipment of research samples and the study drug propranolol. Some insurers will not pay for drugs, tests or hospitalization that are part of research studies, so check with your insurer before you join this study. If you have questions regarding study costs, please contact Dr. Knight.

D2. WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

There is no payment for being in this study.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this study. You are free to say yes or no. If you do not join this study, your doctor can discuss other healthcare choices with you.
Your other choices may include:

- You may continue to transplant without participation in this study
- Joining a different research study

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE STUDY?

If we learn any important new information about the drug that might change your mind about being in the study, we will tell you about it right away. You can then decide if you want to stay in the study.

D5. WHAT HAPPENS IF I AM HARMED BECAUSE I TOOK PART IN THE STUDY?

If you have been following directions, the injury is directly related to the research, and not the result of an underlying condition, then MCW will compensate you for the injury.

If you think you have been injured because of this study, let the study doctors know right away by calling 414-805-6800.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

- If you have more questions about this study at any time, you can call Jennifer Knight, MD at 414-805-6800
- If you have questions about your rights as a study participant, want to report any problems or complaints, obtain information about the study, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this study?

To do this research study, we need your permission to collect and use some of your health information, or you cannot be in the study. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the study.

The health information to be collected and used for this study is:

- Hospital/ Medical Records
- Biological Samples
- Questionnaires

E2. Who will see the health information collected for this study?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the study team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

The study team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this study. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this study, we plan to share information with those doctors, researchers or government representatives working with us on this study at the institutions or companies listed here:

U.S. Food and Drug Administration, Rockville, MD
Any Independent ethics committee, which approved this study
Any Data Safety Monitoring Board appointed to review this study
Other Regulatory Agencies and/or Their Designated Representatives
UCLA Social Genomics Core Staff
Those required by law

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different study without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed, the information might be used or released for other purposes without asking you. Results of the study may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?
One risk of taking part in a research study is that more people will handle your personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the study doctor about whether this could apply to you.

E4. How long will you keep the health information for this study?
If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this study.

E5. Can I cancel my permission to share this health information?
If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Jennifer Knight, MD at *Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226*. The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the study. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE STUDY

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can look up this study by referring to the ClinicalTrials.gov number (NCT02420223) or by asking the study team for a printed copy.

CONSENT TO PARTICIPATE IN THE STUDY

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The study's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the study team use and share the health information and other information gathered for this study.
- I voluntarily agree to participate in this research study. I agree to follow the study procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Legally Authorized Representative (if applicable) *please print*	**Signature of Legally Authorized Representative**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the study team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. In all research study protocols the Principal Investigator is responsible and accountable for the study.*