Information Sheet for Research Subjects

Research Study Title: High Dose Granulocyte Transfusions for the Treatment of Infection in Neutropenia

Principal Investigator: Eliot C. Williams, M.D., Ph.D.

How to contact the study staff: via telephone at (608) 263-1836.

Who to call if you have questions about being a research subject: University of Wisconsin Hospital and Clinics Patient Relations Representative at (608) 263-8009.

This sheet provides key information you need to know about this research study. Taking part in a research study is voluntary. You don't need to take part in this study to receive care for your condition. You can stop taking part in this study at any time without any penalty. Feel free to ask the researchers any questions you have about this study. THE ATTACHED CONSENT FORM INCLUDES MORE INFORMATION ABOUT TAKING PART IN THIS RESEARCH STUDY.

The purpose of the research study:
To see the safety and effects (good or bad) of granulocyte transfusions in treating people who have a serious infection as a result of chemotherapy or stem cell transplantation.

Main procedures you will undergo if you take part in this research study:
- Blood tests.
- Granulocyte transfusions (if you are in the granulocyte treatment group).

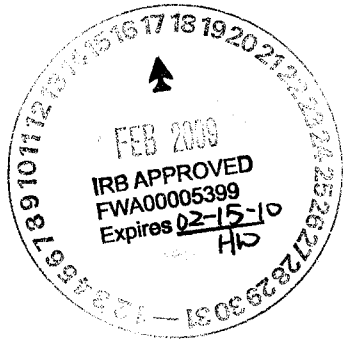
Number study visits and how long study visits will be:
Your participation in the study will take place while you are a patient in the hospital.

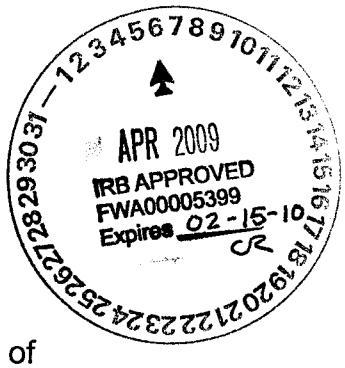
How long you will be in the study:
About 3 months.

Main risks of taking part in this research study:
Risks of blood draws: discomfort at the site of the blood draw with bruising, bleeding, infection, and, rarely, fainting.

Risks of transfusions: fever, chills, shakes, rash, hives; being infected with hepatitis B or C, the AIDS virus (HIV 1 & 2), the HTLV viruses (1 & 2), West Nile virus, or cytomegalovirus; severe allergic reaction.

Possible benefits of taking part in this research study:
We cannot guarantee that you will benefit from taking part in this study. If you are in the granulocyte treatment group, you may benefit from the study if this treatment proves to be effective. In the future, people who have serious infections may benefit from the information learned from this study.





RESEARCH SUBJECT INFORMATION AND CONSENT FORM
University of Wisconsin Comprehensive Cancer Center

TITLE: High Dose Granulocyte Transfusions for the Treatment of Infection in Neutropenia

PROTOCOL: TMH-04

SPONSOR: National Heart, Lung, and Blood Institute

INVESTIGATOR: Eliot C. Williams, M.D., Ph.D.
608-263-1836

SITE: University of Wisconsin Comprehensive Cancer Center
600 Highland Avenue, H4/534
Madison, WI 53792-5153

Name of the Subject History #

Introduction and Invitation

You are being invited to take part in a research study because you have a serious infection and a low granulocyte (white blood cell) count. Granulocytes are very important in fighting infection. Transfusions of granulocytes are sometimes given to help fight a serious infection when the granulocyte count is very low. In this study, you may receive granulocytes along with standard antimicrobial therapy (medications used to fight infection), or you may receive standard antimicrobial therapy by itself. Taking part in this research study is voluntary.

Patients often develop serious infections when their granulocyte counts are very low. A healthy person replaces all the granulocytes in his or her body daily. If a person cannot make his or her own granulocytes, he or she can be given granulocytes from a healthy donor. This is done by transfusion (infusing blood cells from a donor into the patient's blood). In this study, the granulocytes will be obtained from healthy donors who have received a combination of two drugs, G-CSF and dexamethasone, which cause the donor to make large numbers of granulocytes. Granulocyte transfusions may help people with low white cell counts fight infections until their own white cell counts recover.

What is the purpose of the study?

The purpose of this study is to see the safety and effects (good or bad) of granulocyte transfusions in treating people who have a serious infection and low granulocyte count as a result of chemotherapy or stem cell transplantation.

What does the study involve?

There will be up to 236 people enrolled in this study at 10-20 medical centers in the United States. Up to 5 people at the University of Wisconsin Hospital and Clinics may be enrolled. The study will last for up to 42 days and will involve study procedures during your hospitalization and at a study visit 3 months later.

To be eligible for this study, you must have undergone high-dose chemotherapy or hematopoietic stem cell transplantation within the past 60 days. You must also have a low white blood cell count that is expected to remain low for at least 5 days, and a suspected or proven serious fungal or bacterial infection. Your doctor will determine whether or not you are eligible for this study.

If you are eligible and agree to be in this study, a computer program will place you in one of the following study groups:

- Standard antimicrobial therapy with daily granulocyte transfusions.
- Standard antimicrobial therapy by itself.

Neither you nor your doctor can choose the group you will be placed in. You will have an equal chance of being placed in either group. At this time it is not known which of the two treatments is better.

Your treating physician will start antimicrobial (antibiotic) therapy for your infection as soon as it is needed. Antimicrobial therapy is the standard of care for your condition. This means you will receive this therapy whether or not you participate in this study. You may already be receiving antimicrobial therapy before you join this study. The choice of antimicrobial drugs will be made by your treating physician and will not be affected by whether or not you receive granulocyte transfusions.

Granulocyte transfusions are being done as part of this study. Granulocytes are sometimes given in this hospital for serious infections when the white blood count is very low. In many centers they are given regularly in this situation.

During the first part of this study, we will collect information about you for a maximum of 42 days. During this time, we will do the following:

- At the start of the study we will collect information about your medical history.
- We will collect information about your antimicrobial therapy and how well it is working.
- We will draw one teaspoon of blood to check your white blood cell count every day until your body starts making its own granulocytes. This would also be done if you were not taking part in the study. Once your body starts making its own granulocytes, we will check your white blood cell count once a week until Day 42.
- One teaspoon of blood will be drawn at the beginning of the study and again at approximately Days 14 and 42 to see if there are antibodies to white blood cells in your blood.

- If you have a confirmed or suspected aspergillosis infection (an infection due to a fungus), we will also draw one teaspoon of blood at the beginning of the study and again at approximately Days 7, 14, and 42 to test for this infection.
- If you have a bloodstream infection, blood samples (2 teaspoons) will be drawn daily until negative twice in a row and one more time at Day 42 to see how well the treatment is working.
- At 42 days, additional studies will be performed to determine whether the infection has responded to therapy. The nature of these studies will depend on the particular infection, and will be determined by your treating physician.

If you are in the granulocyte transfusion group:
Subjects assigned to receive granulocyte transfusion treatment will be given daily granulocyte transfusions as soon as granulocytes are available. We will try to give granulocytes every day, but there may be days when they are not available. Granulocyte transfusions will be stopped if:
1) Your bone marrow works well enough to make its own granulocytes.
2) You experience serious side effects from the transfusions.
3) Your physician determines that the infection has resolved or improved.
4) Your physician decides to discontinue the study.

If you are in the granulocyte transfusion group, we will do the following:
- We will draw one teaspoon of blood before each granulocyte transfusion to measure the level of granulocytes in your blood. This would also be done if you were not in the study.
- We will draw one teaspoon of blood after each granulocyte transfusion to measure the level of granulocytes in your blood.
- We will check your vital signs and oxygen saturation within 15 minutes before the transfusion of granulocytes, within 15 minutes after the start of the transfusion, and about 1 hour after the end of the transfusion.

Three months after you start this study, we will collect information about your health status by reviewing your medical and/or public records and/or by contacting your physician. If additional information is required, we would like to contact you by telephone.

Some of your blood samples will be sent to a central laboratory in another city for testing. These samples will be discarded after the research is complete. Clinically relevant information (information that could help your physician) might be obtained from the results of these blood tests that are being sent to the central lab. These results will not be shared with you and/or your physician because the results will not be available during this study. Your physician can always order these tests outside of the study if they are needed, in which case the results would be available.

Are there any side effects or risks involved?

Risks related to Blood Draws: The common side effects of blood draws include discomfort at the site of the blood draw with bruising, bleeding, infection, and, rarely,

fainting. However, most of the blood samples will be drawn through your catheter, which minimizes the occurrence of these risks.

Risks related to Transfusions: The major risks of this study are the risks related to transfusion and are similar to those due to any transfusion. These include fever, chills, shakes, rash, and hives (transfusion reaction). They are generally treatable and go away if the transfusion is stopped. Your doctor may be able to give you other medications to prevent or make some of these less bothersome. Although all donor blood is routinely screened for the presence of hepatitis B and C, the AIDS virus (HIV 1 & 2), the HTLV viruses (1 & 2), West Nile virus, and, on occasion for cytomegalovirus, infections with these or other viruses may still occur but are extremely rare. Any transfusion may also cause a severe allergic reaction that could result in a need for resuscitation, intensive care, or death.

Some complications are more likely to occur after granulocyte transfusions than after other types of transfusion. Breathing problems may occur if the transfused granulocytes injure the lungs (known as acute lung injury). This occurs in less than 5% of people. This is generally treatable and reversible and is rarely life-threatening. Your body can also develop reactions against platelets (cells that help blood to clot), which may make it harder to keep your platelet count at a safe level by platelet transfusions. This is also a rare problem. This complication is often treatable with special platelet transfusions. There are no known reproductive risks associated with granulocyte transfusions.

You are at risk for any of these side effects. There may be other side effects that we cannot predict. You should discuss risks and side effects with your physician. Some side effects may lead to stopping therapy with the granulocyte transfusions. Hospitalization may be necessary for treatment of some side effects. As discussed above, the side effects are generally reversible or treatable, but in some cases they may be very serious, long-lasting, and/or life-threatening.

Are there any benefits?

No direct benefit is guaranteed from your participation in this study. However, subjects receiving granulocyte transfusions may benefit from the study if this treatment proves to be effective. The information learned from this study may be of future benefit to others who have serious infections.

What if there are significant new findings?

Information about all significant new findings discovered during the course of this study that may reasonably influence your willingness to continue in the study will be provided to you as it becomes available.

Will compensation be made for any injury resulting from this research?

In the event that you are physically injured as a result of participating in this study, emergency care will be available. You will, however, be responsible for the charges for the emergency care. There is no commitment to provide any compensation for

research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the investigator, Dr. Eliot Williams, at (608) 263-1836 if you are injured or for further information.

Who should I contact for further information on the study, or on the rights of research subjects?

If you have any questions about this study, you may contact the study investigator, Dr. Eliot Williams, at (608) 263-1836. If you have any questions about your rights as a research participant, you may contact the UW Hospital and Clinics Patient Relations Representative at (608) 263-8009.

Are there any costs involved?

You will not be responsible for the cost of the tests done specifically for this study. However, you and/or your insurance company will be responsible for the cost of those tests that would be done as part of your standard care, which in this case are some of the blood tests. If you are in the granulocyte treatment group, you and/or your insurance company will also be responsible for the cost of the granulocyte transfusions, as would be the case if you received them without being in the study.

Will I be paid for participating in this study?

You will not be paid for your participation in this study.

How will my confidentiality be protected?

The centers and doctors in charge of this study will keep your personal information as private as possible. They will do their best to see that it is shared only when required by state or federal law. It is impossible to promise total confidentiality.

Medical and laboratory information obtained from your participation in this study will be gathered by research staff and submitted to a Data Coordinating Center, New England Research Institutes, Inc., for analysis. In the data submitted to the Data Coordinating Center, only an assigned study number will identify you. Your identity will be kept confidential and will be known only to authorized study personnel. All information collected by the researchers from your medical record or from you will be kept strictly confidential and will be used for research purposes only. These records will be stored by your local study investigators in locked files or locked offices. Your name will never be directly connected with information that is collected from you or your medical records. Information that is collected from you or your medical records will be grouped together with other participants' for any reporting of the study findings. In order to understand the results of the study, people from the UW Hospital and Clinics, the Institutional Review Board for the protection of human subjects, and the Transfusion Medicine/Hemostasis Clinical Trials Network Data Coordinating Center may need to see medical records with your name on them. Your research records may also be shown to authorized personnel from the Food and Drug Administration (FDA), and the National Heart, Lung, and Blood Institute. The UW-Clinical and Translational Research Core's

Research Subject Advocate and the Data and Safety Monitoring Committee may also review medical records and other information. Your identifying information would be seen if one of the above-mentioned agencies reviewed your medical records, but your confidentiality would be protected.

Information that does not disclose your name and data collected from you and other study participants will be discussed both with doctors and non-medical personnel. This information may be summarized at scientific meetings or published in medical journals; however, your identity will not be disclosed in those presentations.

If you withdraw from the research study, information that has already been collected will become part of the research data; however, that data will not identify you.

If I decide to start the study, can I change my mind?

Taking part in this research study is voluntary. You may decide not to participate or you may leave the study at any time. Choosing not to participate or leaving the study will not result in any punishment or loss of benefits to which you are entitled. Your decision will not affect your routine medical treatment, your relationship with those treating you, or your relationship with the study staff. If you are assigned to granulocyte therapy and you choose to leave the study, you will continue to receive standard antimicrobial therapy. If you are assigned to standard antimicrobial therapy and you choose to leave the study, you will continue to receive antimicrobial therapy since it is standard care for your condition. In either case, you will still continue to receive standard medical care.

Even after you agree to take part in this study, you may withdraw at any time. Before withdrawing, you should notify one of the people involved with this research. This will allow that person or someone else supervising the research to inform you of any medical risks associated with withdrawing. You can choose to withdraw one of two ways. In the first, you can stop study treatment, but still allow the study staff to follow your care. In the second, you can stop your study treatment and not have any further contact with the study staff. Either way, there will be no penalty to you.

The study doctor, the study sponsor, or the FDA may take you out of the study without your permission at any time if you do not follow the study doctor's instructions, if it is found that you should not be in the study, if the study is stopped, or if it becomes harmful to your health.

Are there any alternatives available to me?

You do not have to take part in this study to receive treatment for your infection. The alternative to taking part in this study would be to receive antimicrobial therapy by itself as standard care. Granulocyte transfusion treatment may or may not be available for people who are not participating in this study. The study staff can discuss your options with you.

You may take time to think this over. Before signing this form, please ask about any aspect of this study that remains unclear. We will attempt to fully answer any questions you may have prior to, during, or following the study.

AUTHORIZATION:

I have read the information in this consent form, reviewed any questions with my doctor or study staff, and I voluntarily agree to participate in this study. I will receive a copy of this entire signed document.

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

_____
Printed Name of Subject Representative*

_____ _____
Signature of Subject Representative* Date

_____
Relationship to Subject*

_____
Printed Name of Principal Investigator or Person Obtaining Consent

_____ _____
Signature of Principal Investigator or Person Obtaining Consent Date

*Only required if subject not presently competent.

Protocol Title: High Dose Granulocyte Transfusions for the Treatment of Infection in Neutropenia

Principal Investigator: Eliot C. Williams, M.D., Ph.D.

Version Date: January 25, 2008

IRB #: H-2008-0051

University of Wisconsin-Madison
Research Authorization Form

Researchers at the University of Wisconsin-Madison (UW) are required to get written permission to use health information from the people taking part in a research study. This permission is called an "Authorization." In order to take part in this research study you must sign this Authorization form.

A. How will my health information be used in the study?

Your health information will be used to help answer the following research question:

- What is the safety and effect (good or bad) of granulocyte transfusions in treating people who have a serious infection and low granulocyte count as a result of chemotherapy or stem cell transplantation?

B. What information will be used?

The following information about your health will be used for this research study:

- Information collected and created during the study.
- Information related to your serious infection and low granulocyte count from your UWHC medical record, including information from tests of your blood or other tissue, and from images produced by x-rays.

C. Who will use my health information?

The people who hold your medical records will share your health information with the UW researchers, who may also share with other people outside the UW. If your health information will be shared outside the UW, those outside institutions and researchers receiving your health information will be listed below.

1. Record Holders:
   - University of Wisconsin Hospital and Clinics Health Information Systems.
   - University of Wisconsin School of Medicine and Public Health, Department of Medicine.
2. Researchers and Others:
   - Researchers and their staff.
   - UW-Madison regulatory and research oversight boards and offices.
   - Research support services.
   - The FDA and other governmental agencies.
   - The Transfusion Medicine/Hemostasis Clinical Trials Network Data Coordinating Center and the National Institutes of Health.

D. How long will my permission last?

This Authorization does not have an end date. You can end this Authorization at any time, however, by withdrawing your permission in writing. Beginning on the date your permission ends, no new health information will be used. Any health information that was shared before you withdrew your permission will continue to be used. After this Authorization ends, you can no longer actively take part in this research study.

Withdrawal of your permission should be made in writing to the person whose name is listed here:

Eliot C. Williams, M.D., Ph.D., Principal Investigator
University of Wisconsin Hospital and Clinics
600 Highland Avenue, H4/534
Madison, WI 53792-5156

E. Is m y permission voluntary?

Your permission is voluntary. You do not have to sign this Authorization form and you may refuse to do so. Your health care providers must continue to provide you with health care services even if you refuse to sign this Authorization form. If you refuse to sign this form, however, you cannot take part in this research study.

F. How will my health information be protected?

Whenever possible your health information will be kept confidential. Federal privacy laws may not apply, however, to some people outside of the UW who can share your health information without your permission. If you signed a consent form to take part in this research, more information about confidentiality protections may be found there.

G. Additional information

You should take as much time as you need to make your decision about giving permission for the use of your health information for this research study. Please ask any questions you have about this Authorization form.

<u>Certification</u>: I have read this Authorization form describing how my health information will be used. I have had a chance to ask questions about the use of my health information and I have received answers to my questions. I agree to the use of my health information for this research study.

_____ _____

Signature of Individual **Date**

_____ _____

Signature of Person Obtaining Authorization **Date**

****YOU SHOULD RECEIVE A COPY OF THIS FORM AFTER SIGNING IT****