

INFORMED CONSENT DOCUMENT

Project Title: Nicotinamide riboside (NR) in Paclitaxel-induced Peripheral Neuropathy

Principal Investigator: Alexandra Thomas, MD
336-716-7217

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have breast cancer. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

We are inviting you to participate in this research study because you have stage 4 breast cancer, are being treated for your breast cancer with Paclitaxel, and are experiencing peripheral neuropathy. The symptoms of peripheral neuropathy include numbness or tingling, pricking sensations or muscle weakness, usually in the hands or feet. However, peripheral neuropathy can also affect other areas of your body.

The purpose of this research study is find out if nicotinamide riboside (NR), a nutritional supplement and type of vitamin B3, can prevent the progression of peripheral neuropathy in people with breast cancer being treated with Paclitaxel.

Nicotinamide riboside is considered investigational as it is being used in this research study, which means that it has not been approved by the U.S. Food and Drug Administration. Nicotinamide riboside is currently used to increase levels of NAD⁺, a substance in the blood which is important in converting blood glucose into energy. Increased NAD⁺ levels may also play a part in delaying the effects of aging, obesity and disease.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 39 people at two different research sites (The University of Iowa and Wake Forest University) will participate in this study, including approximately 20 people at this research site.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last approximately 9 months. This includes up to 12 weeks of treatment with NR, then follow-up visits at the following time points:

- 7-14 days after the end of treatment
- 30-37 days after the end of treatment (may be done by telephone)
- 12-14 weeks after the end of treatment (may be done by clinic visit or telephone)
- 24-26 weeks after the end of treatment (may be done by clinic visit or telephone)

Each visit during treatment will last between 1-2 hours. Each follow-up visit will also last between 1-2 hours. You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT WILL HAPPEN DURING THIS STUDY?**Before you begin the study:**

If you choose to take part in this study, you will need to have the following procedures to find out if you can be in the study. Most of these procedures are part of your regular cancer care and would be done even if you do not join the study.

- A complete physical examination, including assessment of vital signs (temperature, height, weight, heart rate, blood pressure, and respirations or breathing rate).
- Blood tests (approximately 3-4 teaspoons of blood will be drawn and studied for kidney function, liver function, white cells, red cells, and platelets).
- Pregnancy test for females of childbearing potential.
- Questionnaire – one page which asks 11 brief questions about how you're feeling.

During study treatment:

You will take the study drug, NR, by mouth twice a day while you are receiving chemotherapy in this study. If your body tolerates the first dose of NR well during the first week of treatment, the dose will be increased for all the remaining weeks of treatment. The number of weeks you will take the study drug depends on when you join the study, as you will only start taking NR once you develop significant symptoms of peripheral neuropathy. If your peripheral neuropathy starts right away when you're receiving chemotherapy, you will take more doses of NR. If your peripheral neuropathy starts later, you will take fewer doses. You will stop taking NR one week after your last infusion of Paclitaxel.

You will have 12 planned infusions of Paclitaxel as part of your regular cancer care, and you will visit the hospital each week for these infusions. Once you've started taking the study drug, NR, the following tests and procedures will be done at each weekly visit:

- Complete physical exam (only on weeks 3, 6 and 9).
- Assessment of vital signs (temperature, weight, heart rate, blood pressure, and respirations or breathing rate).

- Blood tests (approximately 3-4 teaspoons of blood will be drawn and studied for kidney function, liver function, white cells, red cells, and platelets).
- Blood for research tests (approximately 3 teaspoons of blood will be drawn to check the level of Paclitaxel and NAD⁺ in your blood.) If your chemotherapy drug levels get too high or too low from taking the study drug, you may be removed from this study.
- Questionnaire – one page which asks 11 brief questions about how you're feeling.

We will ask you to complete a questionnaire each time you visit. This questionnaire will ask specific questions about how you've been feeling. We will also provide you forms to keep track of the study drug that you take each day, and how much dairy you eat each day.

After study treatment:

After you've finished taking NR, you will have a follow-up visit 7-14 days after your last dose. The following tests and procedures will be done:

- A complete physical examination, including assessment of vital signs (temperature, weight, heart rate, blood pressure, and respirations or breathing rate).
- Blood tests (approximately 3-4 teaspoons of blood will be drawn and studied for kidney function, liver function, white cells, red cells, and platelets).
- Questionnaire – one page which asks 11 brief questions about how you're feeling.

You will also have follow-up scheduled at the time points listed below. These may be done by a telephone call to see how you're doing.

- 30-37 days after the end of treatment.
- 12-14 weeks after the end of treatment.
- 24-26 weeks after the end of treatment.

Follow-up Contact Plan:

If we aren't able to successfully contact you by telephone, we may send you a certified letter to your last known address, requesting a return receipt.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Blood Draws:

You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Study Drug:

There is a risk that the study drug (NR) will increase or decrease the level of paclitaxel in the blood. An increase in levels of paclitaxel could result in increased peripheral neuropathy and decreased levels of white blood cells and red blood cells. A decrease in levels of paclitaxel could decrease the effectiveness of this chemotherapy. Your levels will be monitored weekly. There is also a very small risk that NR will cause flushing (a sudden redness of the skin.) You may also experience headache, nausea, vomiting, fatigue, dizziness, or loose stool. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Reproductive Risks:

For Females:

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study and throughout the follow-up period. Any of the following methods have been determined to be more than 99% effective (<1% failure rate per year when used consistently and correctly)

- Complete abstinence from sexual intercourse
- Double barrier methods:
 - Condom with spermicide in conjunction with use of an intrauterine device
 - Condom with spermicide in conjunction with use of a diaphragm
- Surgical sterilization (bilateral removal of ovaries with or without hysterectomy, tubal ligation or vasectomy) at least 6 weeks prior to starting the study.
- Non-hormonal intrauterine device (IUD)

We encourage you to discuss this issue further with your physicians if you have any questions.

For Males:

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

Your Health Information:

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe. In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

WHAT ARE THE BENEFITS OF THIS STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: a decrease in the occurrence of your peripheral neuropathy, the chance to obtain the full benefit of your chemotherapy, and a dramatic improvement to your quality of life both during your chemotherapy and in the years that follow.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could choose to have no treatment for your peripheral neuropathy, or choose to take part in a different research study, if one is available.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any additional costs for being in this research study. The study drug, nicotinamide riboside is being supplied by the maker of the drug, ChromaDex, Inc. The cost of blood draws that are done for research only will not be billed to you or your insurance company. However, costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study. However, your parking may be validated for trips made to the outpatient clinic for study related visits.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health (NIH) is funding this research study. The lead coordinating site is The University of Iowa, who is receiving payments from the NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the NIH for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of \$25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of \$25,000 coverage for each claim and is limited to a total of \$250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the

Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Thomas at 336-716-0230 or 336-713-5440 (after hours.)

WHAT ABOUT CONFIDENTIALITY?

To help protect your confidentiality, we will conduct research interventions in private rooms, limit data collection, and store research documents in locked offices and on password-protected computers. Study data will not list your name, but will identify you by a code number. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. If so, your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction. ChromaDex, Inc, the maker of the study drug, may also inspect any part of your medical record for the purposes of auditing the conduct of the study.

The purpose of this research study is to obtain data or information on the safety and efficacy of Nicotinamide Riboside; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a research study. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information (PHI). The information we will collect for this research study includes: physical examination notes, blood test results, vital signs, and personal information collected from study questionnaires.

Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you (“your health information”) may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are listed below. It is possible that these entities may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital
- The Wake Forest University Health Sciences and the University of Iowa Institutional Review Boards (committees that review and approves research studies)
- Representatives from government agencies such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) and the National Institutes of Health (the study sponsor).
- Laboratory staff, auditing departments, and other study representatives from the University of Iowa
- ChromaDex, Inc, the maker of the study drug may also inspect any part of your medical record for the purposes of auditing the conduct of the study.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant’s original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use as evidence any information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding. For example, if there is a court subpoena, the researchers may not disclose your information unless you have consented for its use in this manner.

Information, documents, or biospecimens protected by this Certificate cannot be disclosed without your consent to anyone else who is not connected with the research, except if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases), you have consented to the disclosure (including for your medical treatment), or if it is used for other scientific

research as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institutes of Health, which is funding this project, or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of child abuse and neglect, or harm to self or others. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document, including research data in your medical record.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least seven years after the study is finished. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Thomas that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Alexandra Thomas, MD
Medical Center Blvd.
Winston-Salem, NC 27157

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

What if I Decide to Drop Out of the Study?

If you decide to leave the study early, we will ask you to talk to the study doctor as soon as possible so that you can stop safely. If you leave the study before the final planned study visit, the study doctor may ask you to complete the final visits.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because in our judgment it would not be safe for you to continue, because your condition has become worse, because you are or became pregnant, or because funding for the research study has ended.

WHAT IF I HAVE QUESTIONS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Alexandra Thomas at 336-716-0230 or 336-713-5440 after hours.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at (336) 716-4542 or the Research Subject Advocate at (336) 716-8372.

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed): _____

Subject Signature: _____ Date: _____ Time: _____ am pm

Person Obtaining Consent (Printed): _____

Person Obtaining Consent: _____ Date: _____ Time: _____ am pm