

Section of Hematology and Oncology

**A RANDOMIZED PHASE II PILOT OF TAILORED PREDNISONE REDUCTION
VERSUS USUAL CARE FOR THE TREATMENT OF HYPERGLYCEMIA
DURING R-CHOP CHEMOTHERAPY**

Informed Consent Form to Participate in Research
Rakhee Vaidya M.D., Principal Investigator

SUMMARY

You are invited to participate in a research study. B cell lymphoma can be treated with a group of drugs called R-CHOP (. Sometimes one of the drugs, prednisone, can cause high blood sugar for some patients. This can delay or disrupt their treatment. The goal of this study is to see if lowering prednisone, depending on their blood sugar levels, is safer but works just as well the usual therapy. You are invited to be in this study because you have B cell non-Hodgkin lymphoma. Also, you will be treated with R-CHOP chemotherapy. (R-CHOP stands for rituximab, cyclophosphamide, hydrodoxorubicin (doxorubicin hydrochloride), Oncovin (vincristine) and prednisone) will be in follow-up for five years

Participation in this study will involve treatment of your lymphoma. You will be placed into one of two study groups. One group will be the standard prednisone dose R-CHOP group. The other will be the tailored prednisone R-CHOP group. In the tailored group, the dose of prednisone would be lowered depending upon your blood sugar levels. All research studies involve some risks. Some risks in this study that you should be aware of are common to this type of chemotherapy. They include feeling sick, bruising, low blood cell counts, tiredness and fluid build-up. There is the possibility that you may benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. Some other choices may include standard R-CHOP chemotherapy. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The rest of this form has a detailed description of this study. Please read this form carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Rakhee Vaidya, M.D. If you have questions, suggestions, or concerns about this study or you want to withdraw from the study, her contact information is: [REDACTED].

If you have any questions, suggestions or concerns about your rights as a volunteer in this Rituximab research, contact the Institutional Review Board at [REDACTED] or the Research Subject Advocate at Wake Forest at [REDACTED].

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 B cell non-Hodgkin lymphoma and will be receiving R-CHOP chemotherapy. Your participation is voluntary. Please take your time in making your decision as

to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to find out how reducing one of the drugs in chemotherapy for B cell non-Hodgkin lymphoma effects blood sugar levels, safety, and effectiveness of the therapy. The drug that we will study is called prednisone. While prednisone helps to treat your cancer, it can cause higher blood sugar that may result in complications and/or treatment delays or disruptions. In this study, we will test the effects of decreasing prednisone in R-CHOP. Some patients will receive the standard treatment plan and some patients will receive a treatment plan where prednisone may be reduced. We want to study the effects, good or bad, of each therapy; how each therapy effects blood sugar during treatment; and if reductions in prednisone can result in a better and safer treatment of B cell non-Hodgkin lymphoma.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

There will be 80 people at Wake Forest Baptist Medical Center who will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Pre-study Activities

In this study, you will be treated for your lymphoma. Before the study takes place, we will determine if you can join the study and if you can, you will sign this informed consent form to participate and be registered in the study.

During this time, we will record your medical history, current medicines you are taking, vital signs, and you will have a physical exam. We will measure your tumor with PET imaging or a CT scan, we will take a blood draw to measure your blood sugar levels. We will measure your Performance Status to see how your cancer is impacting your daily life.

Study Activities

In this study you will be randomized into one of two study groups: standard prednisone R-CHOP or the tailored prednisone R-CHOP group. In the tailored prednisone group, the dose of prednisone will be lowered depending on your blood sugar levels. 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.

You will receive chemotherapy in cycles. A cycle of chemotherapy is when you take your chemotherapy and then let your body rest. In this study, a cycle is 21 days (3 weeks). You will take medicine for 5 days and then let your body rest from day 6 to day 21. This cycle will be repeated 6 times.

R-CHOP stands for rituximab, cyclophosphamide, hydrodoxorubicin (doxorubicin hydrochloride), Oncovin (vincristine) and prednisone. Rituximab is a drug that is given to you through your vein during the first cycle. For cycle 2 through cycle 6, rituximab may be given by vein or through the skin. Prednisone is a pill taken by mouth. The remaining drugs are given to

you through your vein. In this study, you will get this therapy for up to 6 cycles (18 weeks). You will give blood before the study, on day 1 before each cycle starts and on day 1 after the drugs are given into your vein to measure your blood sugar levels. If you are in the tailored prednisone group, and your blood sugar level is 200 mg/dL or higher the dose of prednisone will be lowered by 25% for the next cycle. If your blood sugar continues to be 200 mg/dL or higher the dose will continue to lower until half of the original dose of prednisone is reached. For example, if you started at 100 mgs of prednisone, your dose may be lowered from 100 mg to 75 mg to 50 mg, but not lower than 50 mg. If you are in the standard prednisone group, your prednisone dose will not change unless you are having bad side effects to prednisone.

For the chemotherapy cycle (21 days) you will take medicine for 5 days and then not take medicine for about 2 weeks (days 6-21). The cycle is described below.

Cycles 1-6

Day 1

R-CHOP (all chemotherapy)

Days 1-5

Prednisone tablets only once a day.

Days 6-21

Rest (no chemotherapy)

During treatment you will have tests, exams and procedures that are a part of your normal care and would happen even if you were not in the study. You will also have tests, exams and procedures that are only a part of research. You will have PET or CT scans before starting the study and at the end of cycles 3 and 6. After cycle 6 you must have a PET scan. You will have blood drawn before starting the study, on day 1 at the beginning of each cycle, on day 1 after the chemotherapy has been given, and 1 year after the start of treatment. So, you will have two blood draws on day 1 of each cycle; once before your start chemotherapy and one after you finish chemotherapy.

You will fill out questionnaires (forms) that will measure your quality of life. You will do this before treatment starts, at the end of cycles 3 and 6, and 6 months after you complete chemotherapy. We will also ask for blood samples at these time points. Any remaining blood from these samples would be store and used for research that may happen in the future.

IF YOU TAKE PART IN THIS STUDY, YOU WILL HAVE THE FOLLOWING TESTS AND PROCEDURES:

Chemotherapy (possibly given at different dose)

As part of this research study, you will receive chemotherapy through a vein (intravenous) one day and by taking a pill (prednisone) once a day for 5 days. The prednisone dose may be different depending on the study group you are placed in. Those in the tailored prednisone group may have their dose decreased for research purposes.

Blood draws

You will have approximately 1-2 teaspoon of blood withdrawn from a vein 32 times over the course of the year study. The total amount of blood withdrawn during the study will be approximately 68 teaspoons. Up to 20 teaspoons will be part of your normal care and 48 teaspoons of these will be for research purposes. Any left-over blood that is for research purposes will also be stored for future research.

CT and PET scans

You will have a CT or PET scan up to 3 times. You must have a PET scan after cycle 6. You will have a scan before treatment begins and at cycle 3 which may be either a CT or a PET scan. These are a part of your normal care.

Questionnaires

You will fill out questionnaires (forms) that measure your quality of life. There will be 2 forms that will be given 4 times: once before treatment, at the end of cycle 3, at the end of cycle 6, and one year after you start chemotherapy. These are for research purposes.

We can send copies of your test results to your personal doctor. Even if you do not wish to have any of your medical information sent to your doctor, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

☐ Yes ☐ No _____ Initials

Storage of Biological Tissue

If you agree to participate in this study, we will use the left-over research blood drawn (as we described on the previous page) during the study for future research purposes. We will do this before therapy, at cycles 3 and 6, and 6 months after the completion of therapy. This will be used for future research. This samples will be kept and may be used in future research to learn more about other diseases. Your sample will be collected in the Cancer Center at Wake Forest University Baptist Medical Center. The sample will be stored in the CTSI freezers and it will be given only to researchers approved by Rakhee Vaidya, M.D. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. In order to participate in this study, you must be willing to provide this sample for future research.

Your blood sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be performed with your blood sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood will not be given to you or your doctor. The results will not be put in your medical record. The research using your *blood* sample will not affect your care.

Your blood sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about six years, one year on study and we will collect survival follow-up for 5 years

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 ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the chemotherapy and procedures we are studying include:

Risks of Prednisone

Major Side Effects

If any of the following side effects occur while taking prednisone, check with your doctor immediately:

More common:

- Aggression
- agitation
- blurred vision
- decrease in the amount of urine
- dizziness
- fast, slow, pounding, or irregular heartbeat or pulse
- headache
- irritability
- mood changes
- noisy, rattling breathing
- numbness or tingling in the arms or legs
- pounding in the ears
- shortness of breath
- swelling of the fingers, hands, feet, or lower legs
- trouble thinking, speaking, or walking
- troubled breathing at rest

- weight gain

Incidence not known:

- Abdominal or stomach cramping or burning (severe)
- abdominal or stomach pain
- backache
- bloody, black, or tarry stools
- cough or hoarseness
- darkening of the skin
- decrease in height
- decreased vision
- diarrhea
- dry mouth
- eye pain
- eye tearing
- facial hair growth in females
- fainting
- fever or chills
- flushed, dry skin
- fractures
- fruit-like breath odor
- full or round face, neck, or trunk
- heartburn or indigestion (severe and continuous)
- increased hunger
- increased thirst
- increased urination
- loss of appetite
- loss of sexual desire or ability
- lower back or side pain
- menstrual irregularities
- muscle pain or tenderness
- muscle wasting or weakness
- nausea
- pain in the back, ribs, arms, or legs
- painful or difficult urination
- skin rash
- sweating
- trouble healing
- trouble sleeping
- unexplained weight loss
- unusual tiredness or weakness
- vision changes
- vomiting
- vomiting of material that looks like coffee grounds

Minor Side Effects

Some prednisone side effects may not need any medical attention. As your body gets used to the medicine these side effects may disappear. Your doctor may be able to help you prevent or reduce these side effects, but do check with them if any of the following side effects continue, or if you are concerned about

them:

More common:

- Increased appetite

Incidence not known:

- Abnormal fat deposits on the face, neck, and trunk
- acne
- dry scalp
- lightening of normal skin color
- red face
- reddish purple lines on the arms, face, legs, trunk, or groin
- swelling of the stomach area
- thinning of the scalp hair

Risks of Blood Draws

You may have discomfort, bruising and/or bleeding where the needle is inserted. Sometimes, some people get 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).

Risks of PET and CT scans

These procedures are a part of your normal care. The risks of these procedures will be explained to you in detail by your doctor.

Risks of Questionnaires (surveys)

In this study you will be asked how you are feeling and how your cancer and treatment are affecting your life. These feelings may become stronger when you are answering these questions.

Risks of Providing Confidential Information

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. 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.

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.

Reproductive Risks and other Issues to Participating in Research

Due to known 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. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

ARE THERE BENEFITS TO TAKING PART IN THE 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 related to the understanding of how to recognize and treat high blood sugar levels during chemotherapy. .

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have the option of standard R-CHOP chemotherapy. The risks of this therapy are the same as described in the consent form.

WHAT ARE THE COSTS?

All study costs, including the study medication (prednisone only) and procedures related directly to the study (research laboratory draws only), will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility. This will include the cost for the other medications you are taking during the study: vincristine, doxorubicin, rituximab, etoposide, and cyclophosphamide and the standard of care procedures that are performed and care you receive during the study like the PET and CT scans and examinations.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. 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.

The purpose of this research study is to get data or information on the safety and effectiveness of tailored R-CHOP therapy in which prednisone is lowered based on blood sugar values. The results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

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 information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed 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 but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if 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 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.

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.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive a \$15 Visa gift card at cycle 4 and a \$15 Visa gift card at the end of the study for a possible \$30 total for taking part in this study. Parking will be validated for study related visits.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest Baptist Comprehensive Cancer Center. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN 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 [REDACTED].

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 Rakhee Vaidya, M.D. [REDACTED].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes: test results, medicines you are taking, Quality of Life assessments and response to therapies.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and will 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 the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

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

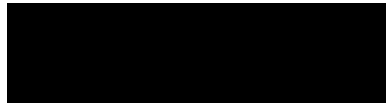
recorded media which are identifiable.

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.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. The authorization does not expire. 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 Rakhee Vaidya, M.D. 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:



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.

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 clinical trial. 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 Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the

research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

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. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Rakhee Vaidya M.D. [REDACTED], this is a 24 hour number.

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 [REDACTED] or the Research Subject Advocate at [REDACTED].

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