The Ohio State University Consent to Participate in Research

Study Title: **Randomized Placebo Controlled Study of Minocycline for Amelioration of Chemotherapy Induced Affective Disorders**

Principal Investigator: Bhuvaneswari Ramaswamy, MD

Sponsor: OSU

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

Improvements in screening and cancer therapies have improved the long-term survival of women with breast cancer, who comprise the largest group of cancer survivors in the United States. Many women with breast cancer tolerate their treatment without difficulty but some do have symptoms that can interfere with their quality of life. These include increased symptoms of anxiety and depression during treatment as well as changes in memory and thinking. Minocycline is an oral antibiotic currently approved by the US Food and Drug Administration (FDA) for the treatment of a variety of infections. As you are currently experiencing brain symptoms of chemotherapy, this study is being done to to investigate if minocycline will help your symptoms during or after chemotherapy.

There is some data that chemotherapy can cause increase in inflammation in the body and the brain. It is possible that the inflammation in the brain is related to the increase symptoms of anxiety, depression and cognitive changes. Promising studies have shown that minocycline may lower inflammatory changes but this will be the first study evaluating minocycline in patients currently receiving or have recieved chemotherapy. With long term use at doses up to 200 mg per day, Minocycline is generally well-tolerated, with the most common side effect being mild gastrointestinal upset. Minocycline readily crosses into the central nervous system and brain where it may help to lower inflammation. Minocycline can be safely combined with chemotherapy and can be administered during chemotherapy as part of the standard of care for the treatment of infections.

Your doctor ordered a chemotherapy regimen to treat your breast cancer and you are experiencing chemotherapy brain symptoms. You are invited to take part in this study to help find out the effects, both good and bad, of minocycline as a possible e treatment for changes in memory and thinking, which can happen during or following chemotherapy.

2. How many people will take part in this study?

Up to 20 patients will take part in this study.

3. What will happen if I take part in this study?

You will need to have the following exams, tests or procedures if you decide to be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. They are being done because you are in this study, in order to better understand how well you are tolerating the study drug.

- Medical history
- Physical exam
- Questionnaires asking about your mood
- Questionnaires asking about your memory and thinking
- Blood tests for inflammatory markers
- MRI (Magnetic Resonance Imaging) scan of the brain A(n) MRI uses radiofrequency waves and a strong magnetic field rather than x-rays to provide clear and detailed pictures of internal organs and tissues.
- PET (Positron Emission Tomography) scan of the brain. A PET scan uses a radiotracer to provide images of internal organ tissues that are more active or more inflamed

As part of the study, you will undergo a history and physical examination including review of your medications and supplements. You will also have a blood test to check levels of inflammation. You will be asked to keep a record of any side effects or changes in your body or health that occur during the study period. You will be asked to complete questionnaires about how you are feeling at baseline, 3 month and 6 month intervals. These are very general questions about any emotional symptoms you have but you do not have to answer any questions that you do not feel comfortable about. These forms will all take approximately 30 minutes and will be done as part of your clinic visit (such as the time when you are waiting for your doctor to see you.) These forms will let us know how you are feeling in terms of anxiety and depression symptoms at the beginning of the study and throughout the study period. You will also have testing to evaluate memory and thinking (neurocognitive testing) at the beginning of the study, at 3 months and at 6 months of study follow up. The blood tests and questionnaires are being performed solely for research purposes. The history and physical examination will be part of your regular follow-up care whenever possible but may be performed solely for the purpose of this study. Imaging studies of the brain (PET scan plus or minus MRI) will be completed per study calendar at the beginning of the study, 3 months and 6 months of the study.

Tests & observations	**Baseline, within 14 days of study start [a]**	**3 months of Minocycline therapy**	**6 months of Minocycline therapy**
Signed informed consent	x		
History and Physical Exam	x	x	x
Height/weight	x	x	x
Clinic visit	x	x	x
Review of medications, supplements	x		
Performance status	x	x	x
Daily Symptom Logs		x	x
Pill Counts		x	x
Minocycline pills (twice daily)		x	x
Neurocognitive testing	x	x	x
STAI and CES-D	x	x	x
Blood Inflammatory markers		x	x
Neuroimging Brain imaging (MRI and PET scans)***	x	x	x

4. How long will I be in the study?

You will take the study drug for 6 months.You will have follow up testing at the end of 3 motnhs and 6 months.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the placebo or minocycline. In some cases, side effects can be serious, long lasting, or may never go away.

Studies using minocycline show that it is overall well tolerated with only few individuals discontinuing therapy due to toxicity and most individuals have no toxicity from drug therapy. Possible side effects from Minocycline are listed below.

Common side effects may include:

- Feeling dizzy or lightheaded
- Mild nausea, stomach upset
- Itching
- Fatigue
- Increased sensitivity to sunlight and potential for sunburn

Rare side effects may include:

- Rash
- Diarrhea
- Joint and muscle pain or stiffness
- Decreased appetite
- Vomiting
- Discoloration of skin, nails, teeth, or lining of mouth Fever
- Hair thinning
- Headache

Very rare but serious side effects may include:

- Symptoms of allergic reaction – hives, trouble breathing, trouble swallowing, swollen tongue
- Inflammation of the lungs which may cause trouble breathing
- Inflammation of the pancreas which may cause pain and inability to eat or drink
- Inflammation of the gastrointestinal tract which may cause pain or diarrhea
- Inflammation of the female genital tract which may cause pain or infection
- Inflammation of the liver which could cause yellowing of the skin or eyes or death
- Ringing in ears or decreased hearing
- Decreased white blood cell (risk of infection), red blood cell (tiredness) and platelet counts (increased risk of bleeding) have been reported
- Harmful kidney effects which may cause decreased urine output or darkening of urine
- Seizures
- Increased pressure inside your head that may cause severe pain or vision changes

Reproductive Risks: Minocycline can cause harm to a fetus when administered to a pregnant woman. Low levels of minocycline are excreted in human milk. Therefore you should not become pregnant or nurse your baby while on this study. If you are not post-menopausal or have the chance of becoming pregnant, a negative pregnancy test is required in order to enroll in this study. If necessary, the costs of this test will be covered by the study. If you become pregnant while on this study, you must notify your doctors and/or the study investigators immediately, and you will be removed from the study. You can ask about counseling and more information about preventing pregnancy.

Blood Draw Risks: You may experience side effects of having your blood drawn. These include pain, swelling, bruising, tissue discoloration or scarring around the vein that is used to draw the blood sample. There is a possibility that some of these tissue changes and scarring could become permanent. There may be the risk of infection at the site where the needle is inserted into the vein. There is also the possibility that you may faint during or shortly after the needle is inserted. If you feel dizzy, you should tell someone and lie down to avoid falling and hurting yourself. These are the same risks that are associated with any blood drawing from your vein. All blood draws will be timed to routine blood work that you would normally get for your chemotherapy visits.

Imaging Risks: This research study involves exposure to radiation from PET scanners using the radiotracer C11(R)-PK11195) and -deoxy-2-[fluorine-18]fluoro- D-glucose (F^{18}FDG).

Psychological Risks: Psychological and social risks are similar to those faced by persons with a history of breast cancer or high risk for developing breast cancer. If you have difficulty with side effects, the researcher and study personnel as well as other physicians and

nurses are available to provide support and necessary information. If on any of the assessments, you have symptoms of depression or anxiety that need immediate attention, you will be evaluated by a counselor/psychologist so that you can be treated for these symptoms and you will be removed from the study.

Neuro Imaging:

Imaging studies of the brain (PET CT plus or minus MRI) will be completed per study calendar at the beginning of the study, 3 month interval and at completion of 6 months of minocycline therapy.

What is Involved:

You will be scheduled at the Wright Center of Innovation (2050 Kenny Road Columbus, OH 43210-3502) for PET CT plus or minus MRI of the brain if you do not have contraindications to MRIs. You will undergo testing for approximately 2 hours if you do both MRI and PET CT testing.

What are the Possible Benefits:

By imaging the brain before, during and after treatment, we can understand better how chemotherapy can affect brain function and whether treatment with minocycline is helpful for reducing these changes.

What are the Possible Risks:

This research study involves exposure to radiation from PET CT scanners using the radiotracer C11(R)-PK11195) and -deoxy-2-[fluorine-18]fluoro- D-glucose ($F^{18}FDG$). The total amount of radiation that each participant will receive for each scan in this study is approximately equivalent to a whole body exposure of 428 days (1.171 years) of exposure to natural background radiation.. This use involves minimal risk and is routinely conducted in other research studies. Patients with metal objects in their bodies or with claustrophobia may have difficulty with the MRI. You have the option of not doing the MRI, but are safe to do PET CT testing.

Please think about your choice. After reading the information above, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse.

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

I choose to take part in the neuro imaging

Yes_____ **No**_____
Initials Initials

PET CT ☐ Both MRI and PET CT ☐

6. What benefits can I expect from being in the study?

You may not benefit directly from participating in the study. Minocycline may reduce symptoms due to chemotherapy. We hope that the information learned from this study will benefit other patients with breast cancer who experience symptoms from chemotherapy in the future.

The minocycline might cause all, some, or none of the side effects listed above. In addition, there is always the risk of uncommon or previously unknown side effects occurring.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

You may choose not to take part in this study. You may choose to receive other investigational therapy, if available. You may choose not to have any treatment at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and ▯
  Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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 the website at any time.

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

10. What are the costs of taking part in this study?

The blood draw and specialized testing is for research purposes only, therefore you and/or your insurance company will not be charged for the research testing. This study will pay for all the research tests.

The following tests and procedures will be done for research purposes only and will not be charged to you or your health plan:

- minocycline
- Blood for Inflammatory biomarkers
- Study questionnaires
- Neurological Imaging including PET and MRIs

All of the other medical tests, evaluations, and procedures are considered standard cancer care and will be billed to you and your insurance plan. You and/or your health plan may also have to pay for other drugs or treatments which are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects. You will be responsible for meeting co-pay and deductible requirements by your insurance plan while on study.

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

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

11. Will I be paid for taking part in this study?

You will be compensated for your time. At all visits, you will receive free parking. In addition, you will receive $50 for completing cognitive testing assessments. You will receive $25 for completing any additional questionnaires with each cycle of chemotherapy. You will receive $150 for completing neuroimaging at each allocated time point. Therefore, you may have an opportunity to receive up to a total of $750. If you are not able to complete the full day visit, your payment will be pro-rated based on the percentage of the visit that you actually completed. Payment will be sent after completing all visits that will ideally be scheduled within about a month; if your visits are more than a month apart, a check in the appropriate amount will be mailed to you within 2-4 weeks of each phase of study completion. If you do not receive your check within 4 weeks after each of these phases of study completion, please notify the researchers. By law, payments to subjects are considered taxable income.

12. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact ***Bhuvaneswari Ramaswamy, MD at 614-293-0066***.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study related injury, you may contact *Bhuvaneswari Ramaswamy, MD at 614-293-0066*.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
	AM/PM
Relationship to the subject	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time