Washington University in St. Louis

INFORMED CONSENT DOCUMENT

Project Title: Randomized Clinical Trial of RANKL Inhibition with Denosumab on Mammographic Density in High Risk Premenopausal Women with Dense Breasts

Principal Investigator: Adetunji Toriola, M.D., Ph.D., MPH

Research Team Contact: Suleepon Uttamapinan – (314) 747-9992

This consent form describes the research study and helps you decide if you want to participate. It 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 and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- 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.

KEY INFORMATION

You are invited to take part in the study called "Randomized Clinical Trial of RANKL Inhibition with Denosumab on Mammographic Density in High Risk Premenopausal Women with Dense Breasts" because you are a premenopausal woman with dense breasts. This is a research study conducted by Dr. Adetunji Toriola looking at whether giving the drug denosumab can decrease breast density. Denosumab is currently approved by the U.S. Food and Drug Administration (FDA) to make bones stronger and prevent fractures. As of now, only one drug is approved to prevent breast cancer in premenopausal women. This study could help us identify an additional drug that could be used to prevent breast cancer in premenopausal women. You should carefully consider the information in this consent document and discuss it with the research team. You should understand why you might want to participate, or why you might not want to participate. The study is sponsored by the National Institutes of Health (NIH). You may choose to participate or not.

If you agree to participate in this study, you will be asked to come in for four study-related visits over the course of 12 months. You will be asked to come to Barnes-Jewish Hospital for the procedures in the study. These will include two injections of the drug denosumab (or placebo) at the start of the study and 6 months after, two breast biopsies at the start of the study and 12 months after, and three or four blood draws at the start of the study, 6 months after, and 12 months after. You will have your regular mammogram as part of your standard care. You may choose to stop participating and withdraw from the study at any time. If you withdraw from the study, the research team may continue to use the information already collected about you unless you inform us that you don't want the information collected about you to be used anymore.

There may be some risks to you if you agree to volunteer for this study. The most common are low

blood calcium levels, and to prevent this, the study team will provide you calcium and vitamin D supplements for the duration of the study at no cost to you. The most serious risk is osteonecrosis of the jaw. This is very rare and resolves once the drug is stopped, but may require treatment in extremely rare cases. Some people are more susceptible to this jawbone problem and we do our best to ensure they do not participate in the study. We will ask you certain questions to determine if there is a risk you might develop this rare side effect while using the drug. We will not enroll you in the study if we determine that you are at risk of developing this side effect. There may also be pain or discomfort at the sites of the blood draw and biopsy. The risks to you are described in more detail later in this consent document. There is no guaranteed direct benefit to you but your participation will help us identify potential new approaches to prevent breast cancer in younger aged women. There is no cost to you. You will be paid a token of $100 at the start of the study, $50 at the 6-month visit, and another $100 at the 12-month visit for your participation.

All of the above information will be further explained and is listed in more detail in the consent document below.

If you decide to take part in this study, you will be asked to sign at the end of this document, after you have had a chance to review all of the information. Do not sign unless you understand the purpose of the study, what you will be asked to do, and the risks that may be involved. The research team will give you a copy of this signed consent document.

Thank you for your consideration.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are premenopausal and have been identified as having dense breasts on a routine mammogram.

Research has shown that there is a link between having dense breasts and the risk of developing breast cancer. Reducing breast density has been shown to decrease the risk of breast cancer. The purpose of this research study is to look at the effects of a drug called denosumab on breast density. If it is shown that denosumab reduces breast density in this study, it will allow us to know whether it can be used for preventing breast cancer in women with dense breasts in the future. In this study, we will look at denosumab in comparison to placebo.

Denosumab is approved by the U.S. Food and Drug Administration to help make bones stronger in women with osteoporosis who have a high risk of fracture. It is also used to prevent bone loss and fractures associated with cancer therapies. However, the use of denosumab is considered investigational in this study.

As of now, only one drug is approved to prevent breast cancer in premenopausal women. This study could help us identify an additional drug that could be used to prevent breast cancer in premenopausal women.

WHAT WILL HAPPEN DURING THIS STUDY?

If you agree to participate, the study team will review your medical history and breast cancer risk factors.
If you are eligible to continue, you will be randomly assigned (by chance, like the flip of a coin) to receive either denosumab or a placebo (saline). You will not know whether you are receiving denosumab or the placebo.

During your participation, you will complete the following procedures and questionnaires :

- You will continue with your routine annual mammogram at the start of the study, 12 months, 24 months, and allow the study team access to your mammogram images. The study team may request access to your routine mammogram at 36 months as well.
- A urine pregnancy test at the start of the study and at 6 months, prior to receiving denosumab.
- Blood draw for research purposes and for limited electrolyte testing at the start of the study, 6 months, and 12 months. You will have about 3 tablespoons of blood drawn from your vein.
- Breast biopsy for research purposes at the start of the study and 12 months. During a breast biopsy, a small cut will be made in the breast and a hollow needle will be used to take out tiny pieces of breast tissue. We do this to look at the effect of denosumab on breast tissue markers. This will help us to understand how denosumab works, if it is found to reduce breast density and breast cancer risk. A small titanium clip around the size of a sesame seed will be placed in the area that was biopsied. Clips are required in the event that a biopsy site requires subsequent excision. Adding a titanium clip is a standard of care for breast biopsies.
- Injection of one 60 mg dose of denosumab or placebo at the start of the study and again 6 months later; this injection will be given subcutaneously (under the skin with a needle) in your upper arm.
- Two questionnaires assessing determinants of breast density and your risk of breast cancer based on your medical history and family history of breast cancer. You are free to skip any questions that you would prefer not to answer.
- A questionnaire approximately 1 week and 1 month after the baseline and 6-month visits, and 1 week after the 12-month visit asking if you are experiencing any medication side effects or biopsy complications.
- A questionnaire approximately 24 month after baseline injection asking if you are experiencing any fracture.
- For one year after your first injection of denosumab or placebo, you will be asked to take calcium and vitamin D supplements by mouth once each day. You will complete brief questionnaires monthly for one year asking about your supplement compliance.

We will be using the blood and breast tissue we collect to study “biomarkers”, which are molecular components that may be associated with the response to denosumab. These biomarkers may be produced from your genes, which are an instruction manual that determines cellular traits.

It is important that you do not become pregnant while you are participating in this study. Denosumab is not safe to take during pregnancy.

Will you save my research information and biospecimens to use in future research studies?

We would like to use the tissue, blood, and data we are obtaining in this study for studies going on right

now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding how to prevent breast cancer, or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your tissue, blood, and data you give up any property rights you may have in the tissue, blood, and data.

We might remove identifiers from your private information and your tissue, blood, and data and then use the information and your tissue, blood, and data for future research studies or share them with other researchers for their future research. If this occurs we will not ask you for additional consent for these uses of your information or tissue, blood, and data.

We will share your tissue, blood, and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

If you change your mind and do not want us to store and use your tissue, blood, and data for future research you should contact the research team member identified at the top of this document. The tissue, blood, and data will no longer be used for research purposes. However, if some research with your tissue, blood, and data has already been completed, the information from that research may still be used. Also, if the tissue, blood, and data has been shared with other researchers it might not be possible to withdraw the tissue, blood, and data to the extent it has been shared.

Please place your initials in the blank next to Yes or No for each of the questions below:

My tissue, blood, and data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My tissue, blood, and data may be shared with other researchers and used by these researchers for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 210 people will take part in this study conducted by investigators at Washington

University.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your active involvement will last for 12 months. During those 12 months, you will have three study visits which could be 1-2 hours in length.

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.

Risks of Denosumab

Likely / Common

- Decrease in blood calcium levels (calcium is important for healthy bones and teeth, as well as for normal muscle and nerve function.)

Rare

- Allergic reactions
- Jawbone problems (osteonecrosis)
- Infections
- Skin problems
- Bone, joint, or muscle pain
- Bone fracture

Risks of Breast Biopsy

The doctor will inform you in detail about the risks associated with the biopsy. In general, having a biopsy can cause pain and swelling. It may also in rare cases cause bleeding and/or infection at the biopsy site. A local anesthetic (to numb the area) may be injected into the skin, or a sedative medication may be given orally or intravenously, but this is very rare. You will remain conscious during this procedure. The risks of an anesthetic are minimal and may include bleeding, bruising, infection, and allergic reaction. If a sedative is used, the risks associated with its use are similar, but also include drowsiness, slurred speech, staggering gait, poor judgment, and slowed reflexes.

Risks of Blood Draw

The side effects of blood draw are very minimal. Possible side effects from a blood draw include fainting, feeling dizzy, pain, swelling, bruising, or bleeding where the needle is inserted. There is also a very small possibility of infection where the needle is inserted.

Risks of Questionnaires

There is a risk you will be asked questions that you find uncomfortable. You have the right to refuse to answer any question.

Risks of Vitamin D and Calcium Supplementation

Taking calcium and vitamin D supplements rarely may cause constipation. Taking a much larger dose of calcium supplements than the instructed dose for this study may lead to side effects associated with hypercalcemia, including nausea, vomiting, and kidney stones.

Risks for Women Capable of Becoming Pregnant

Denosumab is not safe to be taken during pregnancy. Pregnant women are not eligible for this study. You are asked not to participate if you plan to get pregnant during the 12 months of the study. If you believe or know you have become pregnant while participating in this research study, please contact the research team member identified at the top of this document as soon as possible.

If you are a woman capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You must try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to your unborn child, or risks to your unborn child that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. You must tell the doctor if your birth control method fails while you are on the study. If you believe or know you have become pregnant while participating in this research study, please contact the research team member identified at the top of this document as soon as possible. Please discuss with the research team how long you need to wait before becoming pregnant after completing the treatment or procedures on this study.

Risks of Genetic Research

There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans and employers with greater than 15 employees to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance or long term-care insurance.

Risk of Breach of Confidentiality

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study. However, we hope that, in the future, the results of this study could help researchers learn more about ways to reduce breast density and prevent breast cancer.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any costs for being in this research study. You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses.

The study team is providing the denosumab, calcium supplements, and vitamin D at no cost to you.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

You will receive a $100 Target or Walmart gift card at the start of the study, a $50 gift card at the 6-month visit, and a $100 gift card again at the 12–month visit for your participation.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health (NIH) is funding this research study. This means that Washington University 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?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at (314) 286-2668 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

Other people such as those indicated below 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. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Hospital or University representatives to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health insurance company. This information may also be released as part of a release of information request.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The

Institutional Review Board has reviewed and approved this study.
- The Siteman Cancer Center Clinical Trials Office
- The Quality Assurance and Safety Monitoring Committee, to monitor the conduct of this study
- Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

To help protect your confidentiality, we will store all study records in a secured environment or in a password-protected, encrypted storage location. All biologic specimens will be stored in a secured environment and will be labeled with a code number rather than your personal, identifying information. Access to all records and samples will be restricted to the research team only.

The Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital is supported by funding from the National Cancer Institute (NCI). To meet NCI requirements, your protected health information relating to your participation in this study (including your social security number) will be stored in a secure database at the Siteman Cancer Center. This database and also your health care records may be reviewed by Siteman Cancer Center personnel. All information will be securely and confidentially maintained.

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

To further protect your privacy, this research is covered by a Certificate of Confidentiality from the federal government. This means that the researchers can refuse to disclose information that may identify you in any legal or court proceeding or to anyone who is not connected with the research except if:
- there is a law that requires disclosure, such as to report child abuse and neglect, or harm to self or others*;*
- you give permission to disclose your information, including as described in this consent form; or
- it is used for other scientific research allowed by federal law.

You have the right to share your information or involvement in this study with anyone at any time. You may also give the research team permission to disclose your information to a third party or any other person not connected with the research.

If information about you or your involvement in this research is placed in your medical record the information may no longer be protected under the Certificate. However, information in your medical records is protected in other ways.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this

research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

- Access to the questionnaire online

- Reminders regarding follow up appointment, fasting, blood sample, and completing questionnaire
- Miscellaneous information regarding the study

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document.

You should be aware that there are risks associated with sending your health information via email.

- There is always a risk that the message could be intercepted or sent to the wrong email address. To avoid sending messages to the wrong email address, the first email we send you will be a test message to ensure we have the correct email address.
- When using any computer you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.
- Your employer will have access to any email communications sent or received on any electronic devices used for work or through a work server.

Do you agree to allow us to send your health information via email?

_____ Yes **_____ No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

If you decide to leave the study early, we will ask you to let the study team know.

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 investigator might decide to end your participation in this research study earlier than planned. This might happen for no reason or because the study has been canceled.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: (314) 747-9992 or (314) 286-2668. If you experience a research-related injury, please contact: Dr. Adetunji Toriola at (314) 286-2668.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at (800) 438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 04/30/24.

_____ _____

(Signature of Participant) (Date)

_____

(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)

_____

(Name of Person who Obtained Consent - printed)