The Ottawa Hospital Research Institute | L'Hôpital d'Ottawa Institut de recherche

PARTICIPANT INFORMED CONSENT FORM

Title of Study: Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

Local Site Principal Investigator (PI): Dr. Jean Seely 613-737-8899 ext. 19151

Funding Source: ECOG-ACRIN

Sponsor: Canadian Cancer Trials Group (CCTG)

Participation in this study is voluntary. Please read this Participant Informed Consent Form carefully before you decide if you would like to participate. Ask the study doctor and study team as many questions as you like. We encourage you to discuss your options with family, friends or your healthcare team.

Why am I being given this form?

You are being asked to participate in this research study because you have been scheduled or are planning to have a standard screening mammogram.

It is thought that routine examination (screening) of the breast using digital mammography contributes to reducing breast cancer deaths by between 20% and 50% in women between the ages of 40 and 69. Currently, digital mammography is considered the standard technology to screen for breast cancer. In Ontario, screening is offered to women of average risk between the ages of 50 and 74. Some women who are screened are asked to return for further imaging.

Why is this study being done?

This study is investigating whether a new type of x-ray breast imaging system called breast tomosynthesis is as good, or better, at finding breast cancer as digital mammography which is our current standard technology to screen for cancer. It is hoped that the new technology will ultimately reduce the number of women who need to return for more imaging procedures or biopsy when no cancer is present. The tomosynthesis machine that will be used for this study has been approved by Health Canada.

About Regular Digital Mammography

Digital mammograms provide two-dimensional (2-D) flat images of the breast. It is The Ottawa Hospital's current gold standard in early detection of breast cancer in women who show no signs of breast disease. However, traditional or regular digital mammograms are not perfect and cannot detect all cancers.

About Breast Tomosynthesis

Tomosynthesis is a special kind of mammogram that produces a 3-dimensional (3-D) image of the breast by using low dose x-rays obtained at different angles. For tomosynthesis, the breast is positioned and compressed in the same way as for a mammogram but the x-ray tube moves in an arc above the breast. It takes less than 10 seconds for the imaging to be complete. The information from the x-rays is sent to a computer, which produces a focused 3-D image of the breast. The x-ray dose for a tomosynthesis image is similar to that of a regular mammogram. These 3-D images eliminate many of the false abnormalities produced by overlapping tissue seen on regular digital mammogram. It also makes some cancers more visible that can be hidden by normal tissue on conventional mammography.

This study is taking place from Canada, the United States and Argentina. We estimate that a total of 165,000 participants will be enrolled in the study, including 2,466 participants from The Ottawa Hospital Rose Ages Breast Health Centre, at the General Campus.

Please talk to your study doctor or study team about the known benefits and risks of these other options before you decide to take part in this study.

How is the study designed?

If you agree to take part in this study and are determined to be eligible by research staff, you will be asked to read and sign this consent form before you are enrolled in this trial and before any study procedures are performed. At the end of the next section, you will find the study charts, which outlines what will be expected of you if you decide to participate in this trial.

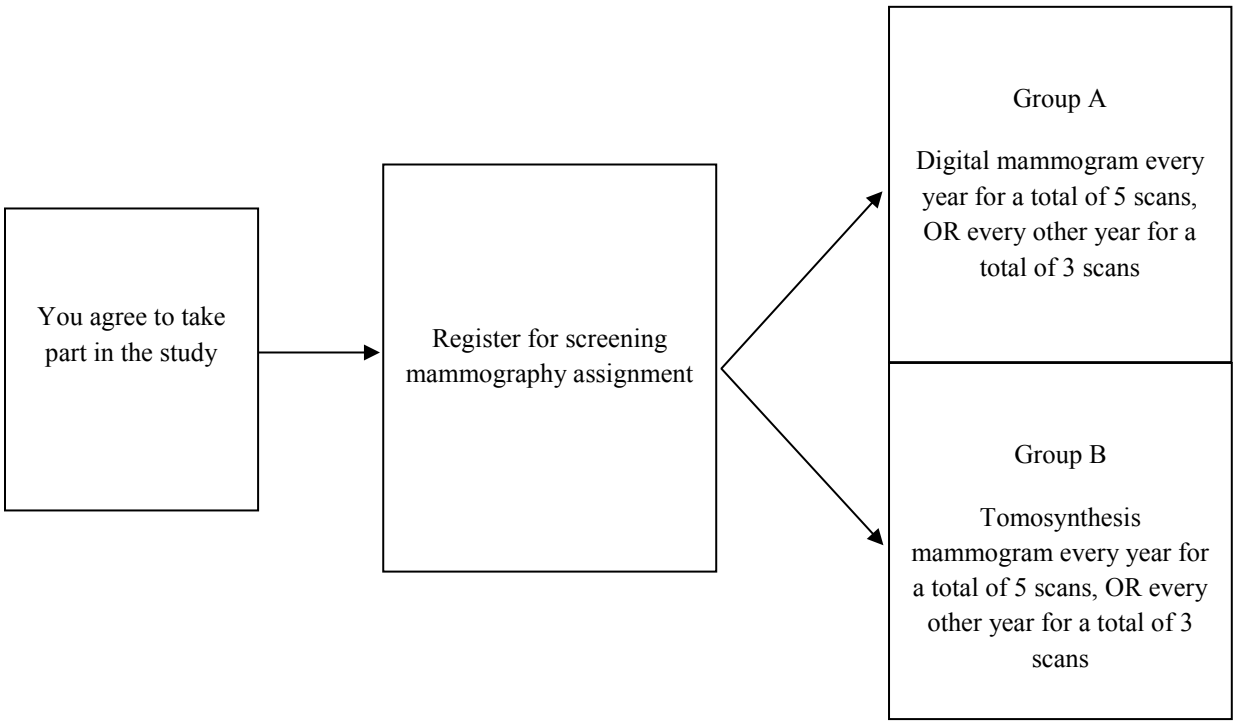
In addition to the tests and procedures listed below, you will also be asked to provide demographic information about yourself as well as details about your medical history. This information will be accessed through your medical chart (in electronic or paper format). You may skip any questions that make you uncomfortable or that you do not wish to answer.

This clinical trial has been designed based on type of screening mammography and screening frequency.

Whether you receive the regular digital mammogram or the breast tomosynthesis will be decided randomly. Randomization means that you are put into a group by chance. It is similar to flipping a coin. A computer chooses which group you are put in. Neither you nor the study doctor or other research staff will choose what group you will be in. You have an equal chance of being placed in any group.

You will be assigned to a screening frequency based on your age, breast density, family history of breast cancer, presence of known breast cancer genes, use of hormone therapy, and menopausal status. You will have a regular Digital Mammogram or a Breast Tomosynthesis either every year for a total of 5 mammograms or every two years for a total of 3 mammograms (please see the figure below for more detailed information.

Your experience during this clinical trial is shown below:



A decision will be made on how often you will receive either digital mammography or tomosynthesis mammography prior to your randomization into a screening mammography study group based on your age, breast density, family history of breast cancer (parent, sibling, or child), presence of known breast cancer genes, prior Lobular Carcinoma in Situ (LCIS) or any type of atypia benign breast disease diagnoses, use of hormone therapy, and menopausal status. LCIS is defined as abnormal cells contained in the milk-producing glands of the breast and atypia is accumulation of abnormal growth of cells in the breast.

You will be informed of the test results after the mammogram has been interpreted by a radiologist at the mammography facility where the mammography was done, or by your physician, depending on the facilities' routine policy.

What is expected of me?

After you consent to participate in the study, you will undergo your screening mammogram with digital mammogram or breast tomosynthesis and the frequency (every year or every two years) of your mammogram will be determined.

Non-Experimental Procedures

The following tests will be done as part of this study. Some of these tests may be done as part of your usual medical care, in which case the results may be used. Some of these tests may be extra, if the interpreting radiologist recommends it based on an abnormal screening mammogram. If the results show that you are not able to continue participating, your study doctor will let you know.

In the event of a public health emergency, the timing of these planned procedures or visits may change. Some visits may happen over the phone or video conference or with your family doctor. Some of the tests that you undergo may be missed, rescheduled or done at other hospitals or laboratories, or may not be done. There may also be changes to your mammogram schedule as well as where and how you receive mammogram. We may also collect information about screening you may have in a public health emergency.

The study team will let you know if changes are required and will make changes if it is safe to do so.

• mammogram

• magnetic resonance imaging (MRI) – a scan that uses a strong magnet to produce pictures of areas inside the body such as organs and other tissue, and inside of bones

• breast ultrasound

• breast biopsy

Central Radiology and Pathology Review

The tomosynthesis mammogram and digital mammogram breast images will be collected as part of this study. This is required for quality assurance and data management. The images will be submitted through a secure electronic image upload system named TRIAD and stored at the ACR Imaging Core Laboratory located in Philadelphia, U.S. for trial quality assurance, in support of imaging and physics study endpoints, and for permanent storage for future imaging based research. If you develop an advanced breast cancer, copies of your imaging reports related to the location of disease will be collected as well. If your imaging was completed at another institution, signing this consent form means that you are consenting to the collection of your imaging reports related to the disease location, together with any related personal health information, from that institution.

To protect your identity, the information that will be on your scans will be limited to your study code.

If you have a breast or lymph node biopsy or surgical procedure during the study, copies of your pathology reports will be collected as part of this study. This is required for quality assurance and data management. The copies along with the biopsy diagnostic slides will be sent to the ECOG-ACRIN Central Biorepository and Pathology, Houston, Texas in the USA, and will be kept for the study unless you do not agree to bank the pathology materials for future research.

To protect your identity, the information that will be on your pathology reports will be limited to trial code and accession number.

To ensure your safety, clinical trials are usually monitored at your centre by the group overseeing the trial to make sure the protocol is followed and side effects are reported. In the event of a public health emergency, the group overseeing this trial may not be able to visit the centre where you are being treated. If this occurs, copies of some documents such as scan reports are already being conducted, but more, such as copies of laboratory reports and clinic reports, may now be collected as part of this study and reviewed by researchers in Canada. The copies will be kept until the end of the study monitoring period when they will be destroyed. To protect your identity, the information that will be on these documents will be limited to your participant study code and initials.

Mandatory Sample Collection

If you undergo either a breast or lymph node biopsy or surgical procedure, a small sample (approximately up to 4mm) of the sample that was biopsied or surgically excised will be collected and analyzed for the purposes of this research study, and will be sent for storage at the Biorepository and Pathology facility at Houston, Texas, USA. You will not be given the results of these genetic tests.

Optional Bio-banking of Leftover Tissue

If you agree, leftover biopsy tissue samples and some related health information will be sent to a biobank and stored until they are used up / destroyed or returned to the hospital where you had your surgery or biopsy. Qualified researchers can submit a request to use the materials stored in the biobank. Your samples and related health information will be used only by researchers whose requests have been accepted by the biobank. The samples and data may be sent to other countries. Your name or any other information that could directly identify you will not be given to researchers.

Specifically, these tissue slides and samples will be sent to a laboratory at the MD Anderson Cancer Center, Houston, TX in the U.S. Slides will be digitally scanned and the scanned copy will be sent to Beth Israel Deaconess Medical Center, in Boston for central diagnostic review. The biopsy tissue and a digitally scanned copy of the H&E slides will be forwarded to the University of North Carolina for genetic and biomarker analysis.

A member of the research team will contact you and/or your treating physician once a year to learn about your health up to 8 years after your final screening round. If anything of concern is detected, your doctors will decide your treatment (for example, diagnostic imaging and/or biopsy), as per the standard of care.

Identification of Samples

To protect your identity, the information that will be on your tissue samples will be limited to the protocol number, your study code, and the pathology accession number.

Withdrawal of Required Samples

If you no longer want your samples to be used in this research, you should tell your study doctor. Your study doctor will notify the sponsor who will ensure the samples are returned to the hospital from which they were obtained if needed, or destroyed. If tests have already been done on your sample(s) it will not be possible to withdraw those results. However, no further testing will be done.

Optional Blood and/or Buccal Cells Samples

You have the option to provide a sample of 10 ml (about 2 teaspoons) of blood and/or the buccal cells (i.e. sample of your cheek cells) that will be used for future unspecified biomarker and genetic research. You will not be given the results of these genetic tests. The blood and buccal samples will be sent in batches to the central repository site at Houston, Texas, USA.

You may choose to not participate in this part of the study. This does not affect your participation in the main study or the care that you receive at The Ottawa Hospital. You will be asked to sign separate consent forms for these sub-studies.

Will my images or research data be used in future research?

Your images and research data will be kept permanently on file at the American College of Radiology Imaging Network (ACRIN). These images will not contain any identifying information and may be used for radiologist training and/or future research that will not specifically help you. If your data and/or images will be used in future studies, approval from a Research Ethics Board will first be sought. ACRIN is mandated by the National Cancer Institute (NCI) to make clinical trial data available to researchers for further research to the maximum extent possible for trials that ACRIN conducts with NCI support. Future researchers would conduct research under their own regulatory requirements and ACRIN may not have any other involvement beyond making de-identified data and images available.

How long will I be involved in the study?

The entire study will last approximately 8 years and your participation in the study will be approximately 8 years. During the first 5 years of your participation in the study, you will be asked to schedule your mammogram and to inform the study team if you undergo any breast imaging test or biopsy at other facilities during this trial. After the first 5 years, you will enter the long-term follow-up phase of the study. You will return to your standard screening schedule. During this time you will be contacted once a year by the study team, who will ask questions about your general health, including possible breast cancer status. Unless you formally withdraw from the study, you will be considered as part of this study. The study team will also perform periodic reviews of your breast imaging records for up to 8 years after your study entry.

Your participation in the study may be stopped for any of the following reasons:

- You are unable to tolerate the study intervention.
- You are unable to complete all required study procedures.
- New information shows that the study intervention is no longer in your best interest.
- Your health changes and your study doctor no longer feels this is the best care for you.
- Canadian Cancer Trials Group decides to stop the study.
- The Ottawa Health Science Network Research Ethics Board withdraws permission for the study to continue.

What are the potential risks I may experience?

While in the study, you may be at risk for the following side effects. You should discuss these with your study and/or treating physicians if they occur. There may be other side effects that we cannot predict. Many side effects go away shortly after the imaging is stopped, but in some cases side effects can be serious, long lasting, or permanent. Your safety is our first priority, and in the event of a public health emergency, your study doctor will discuss any additional risks or changes to your mammogram with you.

Risks associated with Digital Mammography or Breast Tomosynthesis:

- Pain and discomfort from the breast compression;
- Bruising as a result of breast compression;
- Tearing of the skin;
- Fainting;
- Experiencing anxiety.

No matter which group you are assigned to (Digital Mammography or Breast Tomosynthesis), suspicious findings from your screening mammogram may lead to further imaging work-up or biopsy. This may or may not result in the diagnosis of cancer.

Radiation Risk:

The standard Ontario Breast Screening Program screening is typically completed every two years. In this study there are extra x-ray examinations for women who undergo annual screening. These x-rays will expose you to additional radiation.

This research study involves exposure to radiation regardless of which arm you are assigned to. The amount of radiation exposure will be largely dependent of your breast size. Your study doctor can explain how the dose might be higher for denser and larger breasts.

Every time you have a mammogram in this clinical trial, the amount of radiation that you will receive is the same amount that you ordinarily receive from the environment in approximately one month of your ordinary life. This is an acceptable dose. The amount of harm from this amount of radiation is low, and no harmful effects are expected.

While most women experience no harmful health effects, there is a very small possible risk of developing a future radiation-induced cancer from receiving radiation from any examination that uses x-rays. However, the benefit of finding cancer from a mammogram outweighs the very small risk of future cancer from the amount of radiation you will receive in your having a screening mammogram.

If you would like more information about radiation exposure associated with the screening mammography, please speak with your study doctor.

Follow-Up Telephone Call:

You might not like all of the questions that you are asked in the follow-up telephone call. You do not have to answer any questions that make you uncomfortable.

Risks of Insurability:

We will take all reasonable steps to keep your research information confidential. Should someone not involved in the research find out that you took part in this research study, or if you choose to share your results (if they are provided to you), there is a possibility that this could affect your insurability under certain policies of insurance, depending on the exclusions in such policies.

Is there a concern with pregnancy or breastfeeding?

Exposure to radiation may be harmful to a fetus. For this reason, you must inform your study doctor if you are pregnant or suspect that you may be pregnant. If you are pregnant or may be pregnant, you are not able to participate in this study. Once you have completed your pregnancy, you can return for the next screening visit. If you are unsure of your pregnancy status at the time of a return visit for a study screening mammography, you should schedule your screening visit after you have had your next period.

In the event of pregnancy, or suspected pregnancy, you must tell your study doctor immediately. The study treatment will be stopped in order to avoid unknown risks to you or the fetus.

Data Safety Monitoring Board

A Data Safety Monitoring Board which consists of an independent group of experts, will be reviewing the data from this research throughout the study.

Can I expect to benefit from participating in this research study?

Taking part in this study may or may not be of direct benefit to you. The results of the mammogram you undergo will be used by your treating physician for breast cancer screening. Breast cancer screening with mammography has been shown to reduce deaths from breast cancer.

If you are 74 years of age at the time of enrollment, you may not benefit from screening mammography regardless of screening arm. There is limited data on the potential benefit of mammography in women 75 and older.

We hope the information learned from this study will benefit other women during breast cancer screening and diagnosis in the future.

Do I have to participate? What alternatives do I have?

You can choose not to participate in this study. If you choose not to participate, you will still receive your standard of care digital screening mammogram. Your study doctor will discuss these options with you.

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now, and then change your mind later without affecting the medical care, education, or other services to which you are entitled or are presently receiving at the Ottawa Hospital.

If I agree now, can I change my mind and withdraw later?

You may withdraw from the study at any time without any impact on your current or future care at this institution.

- If you decide to withdraw from the study you should contact the study doctor or the study team first. They will discuss the related issues or possible safety concerns for you.
- You may also choose to discontinue your participation in the study. However, a final visit(s) may need to be completed to ensure your safety and well-being.
- If you withdraw your consent, the study team will no longer collect your personal health information for research purposes, unless it is needed for review of safety.
- Information given to the sponsor before you cancel this consent may still be used.

What compensation will I receive if I am injured or become ill in this study?

In the event of a study-related injury or illness, you will be provided with appropriate medical treatment and care. Financial compensation for lost wages, disability or discomfort due to an injury or illness is not generally available. You are not waiving any of your legal rights by agreeing to participate in this study. The study doctor, The Ottawa Hospital and CCTG still have their legal and professional responsibilities.

Will I be paid for my participation or will there be any additional costs to me?

You will not receive payment for taking part in this study.

How is my personal information being protected?

- If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your name, address, telephone number, date of birth, new and existing medical records, or the types, dates and results of various tests and procedures.
- Information that identifies you will be released only if it is required by law.
- All information collected during your participation in this study will be identified with a unique study number (for example participant # AB01), and will not contain information that identifies you.
- Data or images leaving The Ottawa Hospital will only contain the coded study number. All data sent to the headquarters of the ECOG-ACRIN Research Group over the Internet will be coded so that other people cannot read it. All personal identifiers are removed and replaced with the coded study number.
- A Master List provides the link between your identifying information and the coded study number. This list will only be available to Dr. Seely and her staff and will not leave this site.
- The Master List and coded study records will be stored securely.

- For audit purposes only, your original medical records may be reviewed under the supervision of Dr. Seely's staff by representatives from:
    - Canadian Cancer Trials Group (CCTG),
    - National Cancer Institute of the U.S., the organization that oversees U.S. participation in this study,
    - the Ottawa Health Science Network Research Ethics Board (OHSN-REB), and the Ottawa Hospital Research Institute.
- You will not be identified in any publications or presentations resulting from this study.
- Research records will be kept for 25 years.
- At the end of the storage time, all paper records will be shredded and all electronic records will be securely deleted.

Authorized representatives of the above organizations and the organizations listed below may receive information related to the study from your medical/clinical study records for quality assurance and data analysis. Your name or other information that may identify you will not be used. The records received by these organizations may contain your participant code, sex, and month and year of birth.

- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- Central Laboratories who receive your samples for testing or research including ECOG-ACRIN Central Biorepository and Pathology Facility, Houston TX; Beth Israel Deaconess Medical Center, Boston, MA; and University of North Carolina at Chapel Hill.
- Central review imaging centre in Philadelphia, U.S.

All of the organizations listed in the above confidentiality sections are required to have strict policies and procedures to keep the information they see or receive about you confidential, except where disclosure may be required by law. The study doctor will ensure that any personal health information collected for this study is kept in a secure and confidential location as required by law. There are federal and provincial laws that these organizations must comply with to protect your privacy.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

A copy of this signed and dated consent form may be included in your health record/hospital chart.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we do not know what research may be done in the future using your information. This means that:

• You will not be asked if you agree to take part in the specific future research studies using your health information.

• You and your study doctor will not be told when or what type of research will be done.

• You will not get reports or other information about any research that is done using your information.

Any information and/or samples sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries dealing with protection of information may not be as strict as in Canada. However, all study data and/or samples that are transferred outside of Canada will be coded (this means it will not contain your personal identifying information such as your name, address, medical health number or contact information). Any information will be transferred in compliance with all relevant Canadian privacy laws. By signing this consent form, you are consenting to the disclosure of your coded information to organizations located outside of Canada.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. 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.

This research study can be found on the above listed website by using the clinical trial registration number NCT03233191.

Your rights

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

If you decide to stop participating in the study or if your participation has been stopped, your doctor will discuss other options with you and continue to treat you with the best means available.

You may withdraw your permission to use your personal health information for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study. Your study data that was recorded before you withdrew will be used but no information will be collected or sent to the sponsor after you withdraw your permission.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

Do the investigators have any conflicts of interest?

There are no conflicts of interest to declare related to this study. The Principal Investigator is receiving financial payment from the Canadian Cancer Trials Group (CCTG) to cover the cost of conducting this study.

What are my responsibilities as a study participant?

It is important to remember the following things during this study:

- Tell your study team about your current medical conditions.
- Tell your study team if you have any breast imaging tests, biopsy or are diagnosed with breast cancer at any hospital/clinic besides the one where you enroll in TMIST.
- Tell your study team if you are thinking about participating on another research study.

- Tell your study team if you become pregnant while participating on this study.
- Tell your study team about all medications and supplements you are taking.
- Tell your study team about any side effects.

Will I be informed about any new information that might affect my decision to continue participating?

You will be told in a timely fashion of any new findings during the study that could affect your willingness to continue in the study. You may be asked to sign a new consent form.

Who do I contact if I have any further questions?

If you have any questions about this study, or if you feel that you have experienced a study-related injury or illness, please contact Dr. Jean Seely or the study staff at 613-798-5555 ext. 19151 or email TMIST@toh.ca.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed this protocol. The Board considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital. If you have any questions about your rights as a study participant, you may contact the Chairperson at 613-798-5555, extension 16719.

Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

Consent to Participate in Research

- I understand that I am being asked to participate in a research study that compares screening outcomes between tomosynthesis and regular digital mammography.
- This study was explained to me by _____.
- I have read, or have had it read to me, each page of this Participant Informed Consent Form.
- All of my questions have been answered to my satisfaction.
- If I decide later that I would like to withdraw my participation and/or consent from the study, I can do so at any time.
- I voluntarily agree to participate in this study.
- I will be given a copy of this signed Participant Informed Consent Form.

It is important that your personal doctor be aware you are in a research study, as you may be taking a treatment that could affect your health. With your permission, we will notify him/her that you are taking part in this study.

Please read the below items and check "Yes" or "No"	**Yes**	**No**	**Participant's Initials**
I consent to my personal doctor being notified that I am taking part in this study.	❑	❑	
If a breast/ lymph node biopsy or surgery is performed, I agree that sample tissue from the biopsy or surgery can be kept in a bio-bank for use in future health research.	❑	❑	

_____ _____ _____

Participant's Printed Name Participant's Signature Date

Investigator or Delegate Statement

I have carefully explained the study to the study participant. To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.

_____ _____ _____

Investigator/Delegate's Printed Name Investigator/Delegate's Signature Date

Assistance Declaration

Was the participant assisted during the consent process? ❑ Yes ❑ No

❑ The consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, and consent was freely given by the participant/substitute decision-maker.

❑ The person signing below acted as a translator for the participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that the participant/substitute decision-maker has understood the information translated.

_____ _____ _____

Name of Person Assisting (Print) Signature Date