The Role of Pre-deployment Retraction in Decreasing Biopsy Clip Migration During Stereotactic Breast Biopsies

Study Protocol & Statistical Analysis Plan

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Evaluating the position of a breast biopsy clip introducer and whether or not retraction prior to deployment results in less clip migration

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1. STUDY DESIGN / SUMMARY:

This will be a single-center prospective randomized control trial that IRB-approved study. We plan to enroll 250 female patients presenting to UAB for stereotactic biopsy. This study is a prospective will target approximately 250 patients. This will be a HIPPA-compliant randomized control trial planned on spanning approximately six months' time. Patients will be entered into the study only based on their already scheduled stereotactic biopsy procedure. Patients will be informed of the study and they will be offered the opportunity to participate or not participate in the study. Their participation is completely voluntary. This study will not involve any intervention that is not already a part of standard care. Patients will be randomized to two groups, one group that will undergo clip placement with approximately with a 5 mm retraction of the biopsy clip post-placement and one that will involve no retraction prior to deployment.

2. BACKGROUND AND RATIONALLE

Clip placement after stereotactic biopsy in breast imaging procedures has been an important part of breast imaging for years. There have been numerous studies documenting clip migration, and it is now a well-known phenomenon. Numerous case reports describe varying locations of clips following biopsy, some being as much as 5 cm from the biopsy site. This creates a problem in both benign and malignant diagnoses. In the setting of a benign biopsy, a clip remains important to provide correlation with a biopsy finding and the original suspicious mammographic site. In malignant diagnoses, the implication is more significant as the clip provides the localization site for excision. Clip migration has been suspected as the cause of up to 60% margin positivity (vs 0% when localizing the biopsy site by using hematoma identification) in breast cancer cases.[1] Although there have been recommended methods of deployment, vacuuming of cavity, release of compression after biopsy, and first post-biopsy mammography positioning techniques, there has been no prospective study assessing technique of clip retraction prior to deployment. Our hypothesis is that retracting to clip 5 mm before clip deployment will help to decrease clip migration. This will help improved accuracy of biopsy site localization and in cases of malignancy, will allow for less complicated, better localized, and improved results of tumor targeting for surgical resection.

3. OBJECTIVES

3.1 Primary Objective

To determine which method decreases clip migration better, retracting the clip deployment apparatus 5 mm before deployment or not retracting.

3.2 Secondary Objectives

3.2.1 Compare different breast densities (entirely fatty, scattered fibroglandular densities, heterogeneously dense, extremely dense) and their impact on clip migration in both groups (retracted vs nonretracted).

3.2.2 Compare different approaches (lateral, medial, superior) to biopsy and evaluate if they have an impact on clip migration in both groups (retracted vs nonretracted).

3.2.3 Evaluate if thinner or thicker breasts result in more or less clip migration in both groups (retracted vs nonretracted).

3.2.4 Evaluate if patient's age correlates with more or less clip migration in both groups (retracted vs nonretracted).

4. PARTICIPANT SELECTION

This will be a single-center randomized control prospective IRB-approved study. We will enroll 250 female patients presenting to have stereotactic breast biopsy procedures. We will approach all stereotactic biopsy patients (less excluded patients), targeting 300 with the goal of 250 by 1 year.

4.1 Inclusion Criteria

All 18-99 year-old healthy females with recommendation for stereotactic biopsy.

4.2 Exclusion Criteria

4.2.1 If there is no clip present on post-clip mammography, the patient will be excluded from the trial (even if a clip was replaced).
4.2.2 If 2 clips were placed (due to one not being seen initially), the patient will be excluded.
4.2.3 Patients who have undergone reduction mammoplasty will also be excluded as this has been discussed as a potential reason for clip migration[8].
4.2.4 No pregnant females will be included. There will be no males included.
4.2.5 There will be no mentally impaired patients included.
4.2.6 No non-english speaking patients included in the study.
4.2.7 There will be no prisoners included in this study.
4.2.8 Inability to provide written informed consent
4.2.9 Males will not be included.
4.3 Inclusion of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in this trial.

5. RECRUITMENT AND SCREENING

5.1 Recruitment Process

Patients will be presenting to the The Kirklin Clinic at The University of Alabama at Birmingham, Fifth floor Mammography for the purpose of previously recommended stereotactic biopsy. The study coordinator, PI, or participating attending radiologist will arrange the interview and provide all data for entry in a secure web-based research database.

5.2 Screening Process

The study coordinator, PI, or participating attending radiologist will screen potentially eligible patients.

6. PROTOCOL PROCEDURES, METHODS, AND DURATION (LAYMAN'S DESCRIPTION)

After confirmation of patient eligibility, the study coordinator, PI, or participating attending radiologist will obtain written informed consent. The informed consent process may take up to 10 minutes. The patients will be discharged from the study after data has been recorded.

Standard of Care:

The stereotactic biopsy will proceed as normally scheduled. This procedure involves the patient presenting to the fifth floor of The Kirklin Clinic (TKC) at The University of Alabama at Birmingham. Once she checks in, she is escorted to a changing room where she changes into a gown. She is then has brought back to the biopsy suite by the technologist. The technologist reviews the biopsy procedure with the patient. The attending radiologist then is notified and joins the technologist and patient in the biopsy suite. The radiologist reviews the biopsy with the patient and obtains informed consent.

Study protocol:

After informed consent for the procedure, the radiologist will discuss the study with the patient after the patient. The patient will have time to ask questions and the radiologist will provide answers. If the patient expresses understanding and agrees to participate in the study, consent will be obtained in written form on a document separate from her biopsy consent document. This will be placed in a secure location and locked in a cabinet in the mammography department on the fifth floor TKC, accessible only to the PI.

Standard of Care:

The procedure will take place as normally planned with the patient being positioned in craniocaudal (CC), lateral-medial (LM), or medial-lateral (ML) position determined by the radiologist ahead of time. The choice of positioning is decided on by the radiologist based on experience and best pathway to obtain to target. Images are obtained to verify the target location. The skin is cleaned and skin/breast anesthetized. A needle (9 gauge 10 cm Eviva vacuum-assisted needle attached to an ATEC vacuum suction machine) is placed to obtain the sample of the biopsy target. The tissue undergoes x-ray imaging to ensure adequate sampling of tissue. Once sampling is considered appropriate, standard steps are performed in the following manner:

1. After biopsy, the cavity is flushed with sterile saline.
2. Tubing is disconnected to allow for suction of fluid from the biopsy cavity. Samples are retrieved from the collection chamber.
3. ATEC machine is placed on biopsy setting until visualization of x-rayed specimens
4. When samples are determined to be adequately retrieved, the clip will be placed (the same clip will be chosen for all procedures to improve standardization unless the attending radiologist determines another clip would be needed).
5. Biopsy clip is then advanced to the site.

At this point, everything performed will is be routine.

Study protocol:

Arm 1: Advancing the clip to the biopsy site and deploying.

Arm 2: Advancing the clip to the biopsy site and retracting 5 mm and then deploying.

Standard protocol

After imaging is obtained to ensure that the clip is visualized, the introducer and clip are removed together.

Patient is then slowly released from mammographic compression maintaining pressure on the breast for at least five minutes. Slow release of pressure is performed.

The patient is then informed of post-biopsy changes. Pressure is held until hemostasis is achieved and a sterile skin glue is applied to the skin incision at the entrance site of the biopsy needle.

A two-view mammogram is performed with the first image obtained in the same position as the biopsy is performed.

Clip migration will be measured on the post-biopsy mammogram compared to the pre-biopsy mammography exam. Clip migration will be measured by the location of the clip with respect to the biopsy site on the immediate post-clip mammography images. While delayed clip migration has been found in case reports, the number of cases of this phenomenon is not felt to warrant additional mammography exams for this study.[8] The millimeters of clip migration will be measured on the CC view and on the true lateral (ML or LM) views. Although migration usually only occurs in one plane, both planes will be reviewed and if there is migration in two planes, one component factor (Pythagorean Theorem as has been used on prior studies[1]) will be calculated.

We will consider significant migration is anything greater than 10 mm from the biopsy site. The use of 10 mm has been documented on prior studies and will be considered as a differentiation point in this study between significant and nonsignificant movement. A further reason for the use of the 10 mm cut off is that at this institution, Savi Scout devices are commonly used for localization. This device is 12 mm long and can accurately be placed at a location bridging the biopsy site and biopsy clip. Any complications will be reported.

7. RISKS

7.1 Breach of Confidentiality – There is an unlikely potential risk of a breach of confidentiality.

7.2 Radiation – Study participants will be exposed to radiation from the mammography imaging. There is an extremely low risk that the radiation may cause cancer or other radiation effects years after the study. Exposure to the radiation through this study is a part of routine healthcare.

7.3 Risk of an Unexpected Imaging Finding – There is a risk that an unexpected imaging finding could be detected. In many cases, these are of benefit to the patient, such as detection of a unexpected cancer. In some cases, the unexpected finding may be indeterminate, such as a renal mass that is not clearly benign or malignant. Indeterminate findings may need additional workup that will not be covered as a part of this study.

8. PRECAUTIONS / MINIMIZATION OF RISKS

Participants will be monitored by study personnel for risks—physical, psychological, social, economic, and/or legal—that participants may encounter during their participation in this study or as a result of DECT imaging and data collection required in this protocol.

8.1 Breach of Confidentiality – The research team is experienced and will utilize best practices to avoid a breach of confidentiality. The risk of confidentially will be minimized by collecting only the data that is required by the study, labeling all data forms and samples with a coded identifier, and maintaining all study records in locked files or password-protected computer files.

8.2 Radiation – The radiation used in this study is a part of the patient's standard of care. No additional radiation is being used due to the study.

8.3 Risk of an Unexpected Imaging Finding – All of the research DECT liver CTs will be interpreted by a radiologist, a physician with expertise in CT imaging. A formal report will be placed permanently in the electronic medical records. Clinically significant unexpected imaging findings will be communicated by phone with the gastroenterologist, per standard of care at UAB.

9. BENEFITS

If our hypothesis is true that retracting the clip 5 mm before clip deployment will help to decrease clip migration, this will help improved accuracy of biopsy site localization and in cases of malignancy, will allow for less complicated, better localized, and improved results of tumor targeting for surgical resection. If the hypothesis does not hold true, than this method of clip deployment should no longer be used as it does nothing to improve clip migration.

10. ALTERNATIVES

This is not a treatment study. The alternative is to not participate in this study.

11. DATA AND IMAGE ANALYSIS

11.1 Image Evaluation and Analysis: Clip migration will be measured on the post-biopsy mammogram compared to the pre-biopsy mammography exam. Clip migration will be measured by the location of the clip with respect to the biopsy site on the immediate post-clip mammography images. While delayed clip migration has been found in case reports, the number of cases of this phenomenon is not felt to warrant additional mammography exams for this study.[8] The millimeters of clip migration will be measured on the CC view and on the true lateral (ML or LM) views. Although migration usually only occurs in one plane, both planes will be reviewed and if there is migration in two planes, one component factor (Pythagorean Theorem as has been used on prior studies[1]) will be calculated.

11.2 We will consider significant migration is anything greater than 10 mm from the biopsy site. The use of 10 mm has been documented on prior studies and will be considered as a differentiation point in this study between significant and nonsignificant movement. A further reason for the use of the 10 mm cut off is that at this institution, Savi Scout devices are commonly used for localization. This device is 12 mm long and can accurately be placed at a location bridging the biopsy site and biopsy clip. Any complications will be reported.

12. STATISTICAL CONSIDERATION:

This is a single-center prospective randomized study to assess two techniques of clip retraction prior to deployment and to determine which method decreases clip migration better,

retracting the clip deployment apparatus 5 mm before deployment or not retracting. This will help improved accuracy of biopsy site localization and in cases of malignancy, will allow for less complicated, better localized, and improved results of tumor targeting for surgical resection.

12.1 Sample size justification

A total of 250 female patients presenting to UAB for stereotactic biopsy will be randomly assigned as 1:1 ratio to Arm1 (n=125) with advancing the clip to the biopsy site and deploying, or Arm2 (n=125) with advancing the clip to the biopsy site and retracting 5 mm and then deploying. Our hypothesis is that retracting to clip 5 mm before clip deployment will decrease clip migration, e.g. only 20% or less of breast biopsy patients who will have significant migration (greater than 10 mm from the biopsy site) while advancing the clip to the biopsy site and deploying without retracting will have at least of 50% significant migration. This size of 125 in each arm will have 99.9% power to test 30% difference (20% vs 50%) or >90% power to test at least 20% difference in proportion of patients who will have significant migration using one-sided Fisher's Exact test at 5% significant level (Table 1).

Table 1 Statistical Power to Test Differences Between Two arms.

Significant migration in Arm1 (%)	Significant migration in Arm2 (%)	Type I error (%)	Power (%)
50	15	5	100
50	20	5	99.9
50	25	5	99.1
50	30	5	93.1
50	15	1	100
50	20	1	99.6
50	25	1	95.4
50	30	1	78.5

A sample size of 125 will also produce two-sided 95% confidence interval to estimate the mean distance of migration with 0.177 standard deviation to the limits for each arm. Patients enrollment is expected to be completed within one year.

13.2 Statistical analysis plan

The primary objective of the number and percentage of breast biopsy patients whose clip has greater than 10 mm from the biopsy site as significant clip migration will be estimated and two-sided 95% confidence interval will be calculated using the method of Clopper–Pearson interval for each arm separately. Fisher exact test will be used to examine if there is significant association between arms in proportion of significant clip migration. The average of distance of clip migration will be estimated with two-sided 95% CI for each arm separately using normal approximation. Two-group student t-test will be used to evaluate the mean difference in the distance of migration from the original biopsy site between arms.

Correlation between migration and breast densities (entirely fatty, scattered fibroglandular densities, heterogeneously dense, extremely dense), different approaches (lateral, medial, superior) to biopsy, if thinner or thicker breasts and age under procedure of retracted (arm2) vs nonretracted (arm1) will be evaluated in two ways for the secondary objectives. First, we will consider significant clip migration (yes, no) as binary outcome. Analysis of Variance method (ANOVA) will be used to compare age differences with controlling of procedures, and Cochran -Mantel-Haenszel Test will be

used to compare differences in categorical variables, e.g. breast density stratified by retracted (arm2) vs nonretracted (arm1). Logistic regression analysis will be explored to identify significant factors associated with clip migration. Odds ratio and two-sided 95% CI will be presented for each factor significantly contributed in the model. Second, we will consider distance of clip migration (mm) as continuous outcome. ANOVA will be used to evaluate the strength of association (beta coefficient in the regression model) and identify significant of factors associated with the distances of migration.

All analysis will be carried out with Statistical software SAS v9.4.

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CONSENT FORM

TITLE OF RESEARCH: **The role of pre-deployment retraction in decreasing biopsy clip migration during stereotactic breast biopsies**

IRB PROTOCOL NO.: IRB-300005277

INVESTIGATOR: Stefanie Woodard, DO

SPONSOR: UAB Department of Radiology

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of the study is to see if the technique used to place the breast biopsy clip, which is a tiny piece of titanium used to identify the site of your biopsy, can reduce the movement of the clip after the placement.
Duration & Visits	You will be in this study for one visit. This visit will last up to two hours.
Overview of Procedures	This study will include the standard of care breast biopsy. You will be randomized (like a flip of a coin) to one of two groups. In one group, a clip deployment device will be inserted and clip placed. In the second group, 5 mm of withdrawn of the device will be performed prior to clip deployment. Both techniques are currently used by physicians. We will not know prior to you consenting to participate which group you will be assigned.
Risks	The most common risks include bruising and swelling in the breast, infection or bleeding at the biopsy site. The clip may or may not be placed correctly at the biopsy site regardless of the technique.
Benefits	You may or may not benefit from this study, but the information may be useful is helping improve breast biopsies in the future.
Alternatives	If you do not want to take part in the study, you will continue your treatment and imaging ordered by your doctor without any consequence.

Purpose of the Research

We are asking you to take part in a research study. The purpose of this study is to compare two techniques used to place a clip during a breast biopsy procedure. We are comparing if the technique used to place the breast biopsy clip could reduce the movement of the clip.

This study will recruit 251 patients from the University of Alabama at Birmingham.

Explanation of Procedures

You have been referred to diagnostic mammography to have a procedure called a breast biopsy. You will be seen by a Breast Radiologist as a part of your routine clinical care.

There will be no special test or scans related to this study. You will receive standard of care treatment. By deciding to participate in this study, you are giving permission for the Principal Investigator and staff to review your medical records.

If you take part in this study, you will be assigned to one of two groups:
the clip is placed by inserting the clip-placing instrument into the site of the biopsy then withdrawing it by 5 mm where the clip is placed.the clip is placed by inserting the clip-placing instrument into the site of the biopsy where the clip is placed without withdrawing the instrument.
You will be randomized (like a flip of a coin) to one of the groups. Both techniques are currently used by physicians. We will not know prior to you consenting to participate which group you will be assigned.

The breast biopsy procedure you will be undergoing is the standard of care stereotactic (mammographic-guided) breast biopsy. It will involve cleaning the skin and making the area numb by injecting numbing medicine with a small needle. The area of concern in your breast will be identified and a needle will be placed into the breast to obtain a small sample of breast tissue. After we complete the biopsy, the clip will be placed using one of the two techniques described above. Biopsy clip placement is standard of care for all breast biopsies. There are different ways to place the clip and we will be using one of two ways to place the clip in your breast. Both methods are used by many different doctors. At the end of the procedure, we perform a post-biopsy (two-view) mammogram, which is also standard of care for every biopsy.

Your participation in this study will only be one visit. The visit will be your standard of care breast biopsy at The Kirklin Clinic (TKC). When you arrive at the TKC the research staff will be available to answer any questions regarding the procedure and consent form. This will take approximately 30 minutes. After you have signed the consent the breast biopsy will take up to one hour.

Risks and Discomforts

If you decide to participate, you will be assigned to a treatment arm (retracting the clip and not retracting) by chance, like the flip of a coin. The treatment you are assigned may prove to be less effective or have more side effects than the other study group or alternatives; however, both treatment arms are routinely used in patient care. Regardless, the general risks of breast biopsies include: bruising and swelling in the breast, infection or bleeding at the biopsy site. The clip may or may not be placed correctly at the biopsy site regardless of the technique. As far as anyone knows, these risks are equivalent for both techniques.

Benefits

You may or may not benefit directly from taking part in this study. However, this study may help us better understand how to improve breast biopsies in the future. This may also ultimately improve the outcomes for patients with breast cancer.

Alternatives

The alternative is to not take part in this study.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What protected health information may be used and/or given to others?

All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of any kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills; any other information related to or collected for use in the research study, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes; records about any study drug you received or about study devices used; and consent forms from past studies that might be in your medical record.

Your consent form will be placed in your medical record at UAB Health System or Children's of Alabama. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your EMR may indicate that you are on a clinical trial and provide the name and contact information for the principal investigator.

If you are receiving care or have received care within this health system (outpatient or inpatient), results of research tests or procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing medical record.

If you have never received care within this health system (outpatient or inpatient), a medical record will be created for you to maintain results of research tests or procedures.

All information within your medical record can be viewed by individuals authorized to access the record.

Who may use and give out information about you?

Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?

All individuals/entities listed in the informed consent document(s), including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere). Your information may also be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the

sponsor, or are owned by the sponsor, or are providing support to the sponsor (e.g., contract research organization).

Information about you and your health which might identify you may be given to:

- the Office for Human Research Protections (OHRP)
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- the University of Alabama at Birmingham - the physicians, nurses and staff working on the research study (whether at UAB or elsewhere); other operating units of UAB, UAB Hospital, UAB Highlands Hospital, University of Alabama Health Services Foundation, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the UAB IRB and its staff
- the billing offices of UAB and UAB Health Systems affiliates and/or Children's of Alabama and its billing agents

Why will this information be used and/or given to others?

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others. Including others outside of UAB, without your permission.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution.

You may be removed from the study without your consent if the study doctor decides it is not in the best interest of your health, or if the study is terminated early.

Cost of Participation

There will be no cost to you for taking part in this study.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Participation in Research

You will not receive payment for participating in this study.

Payment for Research-Related Injuries

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, you may contact Dr. Woodard. She will be glad to answer any of your questions. Dr. Woodard's number is 205-801-7735. Dr. Woodard may also be reached after hours by paging at 205-934-3411.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above, have had a chance to have all of your questions answered, and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Printed Name of Participant

_____

Signature of Participant Date

_____

Signature of Person Obtaining Consent Date