LCCC1853: Novel MRI sequence- MR Fingerprinting in Breast MRI- Feasibility study

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Date of Protocol: October 30, 2018

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1. BACKGROUND AND RATIONALE

1.1. Study Synopsis

The ultimate goal of this proposed study is to evaluate potential clinical efficacy of a novel magnetic resonance imaging (MRI) approach, MR fingerprinting, capable of providing quantitative measures of important tissue properties, which could provide important insights into normal breast tissue. We will recruit a totally of 30 patients scheduled for screening breast MRI for high risk normal patients. The novel sequence, namely MR fingerprinting, will be added prior to the injection of MR contrast, followed by the rest of the clinical imaging sequences. Quantitative maps, including T1, T2map will be computed from MR fingerprinting.

1.2. Disease Background

In clinical setting, breast DCE MRI was performed for breast cancer staging, high risk screening, and problem solving when mammography, ultrasound and clinical findings were questionable. The protocol for screening MRI and clinical breast DCE MRI were the same. Patients were put on prone position with bilateral breasts fit in the dedicated breast coil. The following sequences will be taken: whole breast axial T1 weighted 3D SPGR, axial T2 weighted FSE with fat saturation, followed with axial 3D T1-weighted fat-saturated DCE MRI with one pre-contrast and three post contrast enhanced phases at the temporal resolution of 100 seconds followed with a high spatial resolution interview scan (0.9 mm isotropic 3D T1-weighted fat-saturated scan). DCE MRI has high sensitivity for breast cancer detection (95%) while lack of specificity (37-86%) between tumor types as overlap between findings of benign and malignant lesions and among different breast cancer subtypes [1]. Specifically, DCE MRI is also a powerful tool for neoangengenesis evaluation or treatment response monitoring for breast cancer [2], with physio- pathologic measurements of the volume transfer constant (K^{trans}), fraction of extracellular extravascular space (v_e), and vascular density (v_p) [3]. To obtain these pharmacokinetic parameters, a relation between the signal enhancement and contrast agent concentrations is required. The native T1 ($T1_0$) is calculated and then used to convert the signal enhancement curve to concentration curve [3]. The most commonly used method to measure T1 is variable flip angle (VFA) imaging which uses several short-repetition-time radiofrequency spoiled gradient-echo acquisitions with varying FAs [4-7]. However, the T1 measurement using VFA has been notified to be marked deviated up to 50% by the nonuniformity of the transmit radiofrequency (B_1) field even in 1.5 T [8]. It would be very important to obtain the most accurate $T1_0$ value of breast tumor before contrast medium injection to calculate the most accurate pharmacokinetic parameters across different platform, vendors and machines. Nevertheless, it is a daunting task to obtain quantitative measures of $T1_0$ independent of these potential confounding factors. The current paradigm of MRI is to use a set of scanner settings to generate an image 'weighted' a specific MR contrast mechanism (physical

parameter), where it is hoped that variations in the parameters will be accentuated. However, without quantitative knowledge of the parameters, the final image contrast may depend on many factors, which may complicate image interpretation and diagnostic performance [9]. Quantitative measurement can provide a great deal of information about tissue properties and pathological conditions, since these parameters ultimately determine the contrast that is observed in conventional images [10]. The investigational imaging sequence, MR fingerprinting, could be performed in a much shorter scanning time and provide more accurate quantitative tissue characteristics (T1 and T2 value).

Despite the irreplaceable roles of breast DCE MRI in clinical practice (most sensitive and accurate in breast cancer detection and staging, and even provide more insight on the perfusion and functional change in treatment response monitoring before the tumor size change in patient undergoing chemotherapy or target therapy), MRI has been pushed to its limit today. One of the principle limitations is that lack of quantitative information for tissue/structure characterization.

MR fingerprinting could be performed in a short time to obtain more accurate quantitative tissue characteristics (T1 and T2 value) simultaneously which would largely decrease examination time (which means reduce patient scanning time in the MR scanner, that is decreased patient suffering time on examination table and decrease examination expanse of hospital).

1.3. Conventional Imaging Modality

The clinical DCE MRI of breast have been widely used for breast cancer screening, detection, staging and treatment response monitoring for decades. This image modality outperforms mammography and ultrasound of breast in breast cancer detection and extent evaluation [11]. There is no radiation risk for this imaging examination. The only two drawbacks of this study are longer examination time and gadolinium based contrast medium usage. The patients need to be rested on the examination table in a fixed prone position (not very comfortable) with bilateral breasts been fitted in the breast coiled for at least 30 to 40 minutes.

As part of the MRI procedure subjects may receive a contrast agent called gadolinium. Gadolinium makes it easier to see details on the MRI pictures. An extremely rare disease called Nephrogenic Systemic Fibrosis (NSF) is associated with the use of gadolinium contrast agents in patients with chronic severe renal insufficiency or renal dysfunction due to hepato-renal syndrome or in the peri-operative liver transplantation period. Exclusion criteria for this study are in compliance with the Food and Drug Administration's advisory statements. If subjects have any problems with their kidneys, they may be at risk for a condition called Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy. NSF has been reported to occur between 2 days and 18 months following injection of gadolinium. There is no known treatment for NSF. Some people have even died from this. Signs and symptoms of NSF may include: burning, swelling, hardening or tightening of the skin, blood vessels and internal organs (heart, lungs, liver; yellow spots on the white part of the eyes; joint swelling and stiffness; pain in the hip bones or ribs; muscle weakness.

Subjects' study doctor will check how well their kidneys work before they are given gadolinium. Depending on how well their kidneys work, they may be given a reduced dose or they may not be able to take gadolinium at all. NSF has not been reported in people with normal kidneys.

1.4. Investigational Imaging Modality

The purpose of this study is to evaluate the novel quantitative MRI techniques, namely MR Fingerprinting (MRF), in clinical studies to determine whether they can provide better, faster, and more useful tissue information for clinical diagnosis. The MRF does NOT require gadolinium contrast medium injection, and will be acquired in about 6 minutes scanning time before the clinical contrast enhancement examinations and 6 minutes at the end of study. This work has been published in Nature for its accurate quantification of proton density, T1, T2 relaxation times in the rapid multi-parametric MR technique[12]. Pilot studies with scans from hundreds of patients have demonstrated that the novel method can provide valuable information for various diseases in brain, liver, and prostate [13-16]. While it has shown great promise in these previous studies, clinical evaluation of this technique has been limited to a few medical centers worldwide due to complexity in installation, implementation and post-processing of the technique. Dr. Yong Chen, a newly recruited faculty at Department of Radiology, is a key developer of the MR Fingerprinting technique[16]. In this study, we propose to apply this novel technique at UNC and evaluate its performance for different conditions of breasts. We hypothesis that the quantitative MR imaging technique will lead to improved tissue characterization, diagnosis and quantification.

1.5. Rationale

This is a feasibility study of the use of the additional MRF scanning sequence with a total of 12 minutes scanning time to our clinical screening breast DCE MRI examination before contrast medium injection and at the end of scan. This additional scanning sequence may provide faster and better quantitative tissue characterization comparing to conventional MR sequences. There is no investigational contrast agent in this study. We propose that the additional MRF sequence may provide faster and more accurate tissue characteristics imaging for clinical evaluation of breast tissue. Patients will be enrolled in with scheduled high risk screening DCE MRI (n=30). The MR imaging will be performed in the clinical 1.5T MR scanners in UNC as normally done for the patients MRI schedule. We only add an additional MRF sequence within the MRI exam just prior to the contrast enhancement scan.

Quantitative measurement of the breast tissue will be performed after the MR exam. The ROI of normal breast parenchyma was recorded. The ROI will be saved and encoded to the T1 map, T2 map in MRF, T1 weighted imaging, T2 weighted imaging. A large variety of imaging ROI-based quantitative measures will be calculated among normal glands in bilateral breasts to evaluate different ROI characteristics among different patients and between bilateral breasts in each patient.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The purpose of this study is to evaluate the novel quantitative MRI techniques, namely MR Fingerprinting (MRF), in clinical studies to establish the T1 and T2 value baselines of normal glandular tissue.

2.2. Primary Endpoint

The normal breast tissue T1, T2 value will be used to compare between sides in same patient and among the different patients and between two MRF sequences in pre-contrast phase and post contrast enhancement phase and also the differences between pre and post contrast enhancement phases.

3. PATIENT ELIGIBILITY

3.1. Inclusion Criteria

3.1.1. English-speaking patients

3.1.2. Ages 18 to 99 years old

3.1.3. Scheduled to undergo a screening breast MRI study

3.1.4. Capable and willing to provide signed informed consent

3.2. Exclusion Criteria

3.2.1. Claustrophobia

3.2.2. Presence of pacemaker, intracranial aneurysm clip, bladder stimulator, cochlear implant or metal near eyes or near pelvis that would create excessive imaging artifact

3.2.3. Known hypersensitivity to [contrast agent] or to any component of [contrast agent] refractory to standard medications (antihistamines, steroids)

3.2.4. Impaired kidney function (serum creatinine level > 1.8 mg/dl or a glomerular filtration rate < 60 as approximated using serum creatinine levels) unless anuric and on dialysis.

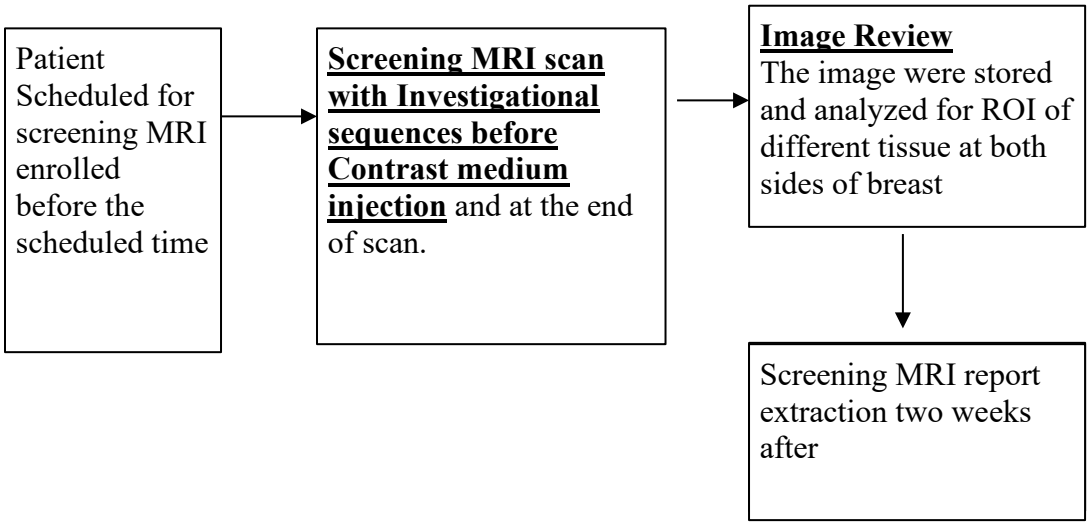
3.2.5. Inability to **tolerate** MRI **(e.g.,** inability to lie **flat** for **>1 hour)**

3.2.6. Pregnancy or lactating female

3.2.7 Previous history of mastectomy.

4. STUDY PLAN

4.1. STUDY SCHEMA



4.2. Study Procedures

The patients will have a set of additional research scan of no more than 12 minutes scan time (MRF) within their primary screening breast MRI study. Patient will receive their standard clinical care as usual. No follow up needed for this observational study.

4.2.1. Enrollment/Recruitment

A total of 30 women will be enrolled to this study. The 30 study subjects will be consecutively recruited from women who are scheduled to undergo a screening MRI. Eligible patients will be identified by research staff review in coordination with the UNC Breast Clinic.

Once a patient has been referred, the patient will be approached by a coordinator from Radiology to assess interest in participation.

All eligible women who agree to participate in the study will be asked to come to their MRI appointment thirty minutes early to complete the informed consent process.

Review of the consent will take place in the privacy of an exam room, or when possible, a sample consent form will be sent to the patient via email prior to the patient's visit to allow for ample review.

4.2.2. Research Imaging

4.2.2.1.Imaging Procedures

The investigational MR protocol will be implemented on the existing MR scanners without any modifications to the existing, FDA approved machine,

equipment, or safety standards. Patients will receive their standard of care imaging. During the screening scan, they will receive the research sequence. The additional sequences will be performed at no cost to the patient other than a small increase in the amount of time spent inside the MR scanner. The additional sequences are 12 minutes in total and do not place individuals at any increased risk.

4.2.3. Standard of Care Biopsy

Almost all of the patients undergoing screening MRI do not have breast cancer. No further intervention with biopsy in this screening population. There is no change of standard of care for the screening population.

4.2.4. Medical Record Abstraction

The breast MRI report will be extracted one week after completion of the MRI exam for confirmation of normal status.

4.3. Time and Events Table

	Pre-study 30 minutes before MRI	Time Point 1 At MRI exam	Time Point 2 1 week After MRI exam	Time Point 3 After 30 cases completed MRI
Informed Consent	X			
Breast MRI with research MRF		X		
Medical Record Abstraction			X	X
Imaging analysis				X

*Include any necessary notes detailing specifics of procedures outlined in table.

5. INVESTIGATIONAL DEVICE

5.1. Investigational Device Description

Investigational sequences will be developed at UNC. The proposed study will be performed on the 1.5T MR scanners: (1) Main campus Siemens Avanto, Invivo 7-channel; (2) Out-patient Imaging center: Siemens Magnetom Aera, Sentinelle Coil. The scanners are FDA approved and all new sequenced

possess the same safeguards as standard (FDA approved) clinical sequences to prevent harm to subjects. The study does not need any contrast administration unless it is required for standard clinical examination. For each consented subject, the additional scans will add no more than 12 minutes to the total scanning time. That is 6 minutes with two MRF sequences (3 minutes on each MRF sequence) pre-contrast enhancement phase and 6 minutes with two MRF sequences at the end of post contrast enhancement phase.

The investigational MR protocol will be implemented on the existing MR scanners without any modifications to the existing, FDA approved machine, equipment, or safety standards. Patients will receive their standard of care imaging. In addition, they will receive the research sequence. The additional sequences will be performed at no cost to the patient other than a small increase in the amount of time spent inside the MR scanner. The additional sequences are no more than 12 minutes and do not place individuals at any increased risk.

The research images will not be interpreted or analyzed for clinical decisions related to the patient. As such, this study will request that the IRB make a determination that this study is no greater than minimal risk. This study meets all the requirements for an NSR determination including:

- The device will not be implanted.
- The device is not intended to support or sustain human life.
- The device is not being used of substantial importance in diagnosing, curing, mitigating, or treating disease.
- The device does not present a potential for serious risk to health, safety, or welfare of a subject.

5.2. Expected Risks

The additional sequences are no more than 12 minutes and do not place individuals at any increased risk.

6. UNANTICIPATED CONCERNS

6.1.1. Unanticipated Adverse Device Effect (UADE)

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)).

6.1.2. Unanticipated Problems (UP)

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.1.3. Reporting

6.1.4. UADEs

UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

For this device study, investigators are required to submit a report of a UADE to the FDA, the manufacturer of the device and the UNC IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)), using the MedWatch Form 3500A. Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, the UNC IRB, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

For this device study, we will submit a report of a UADE to the manufacturer and the IRB as soon as possible, but no later than 10 working days after the investigators first learn of the event.

6.1.5. UP

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

Any <u>unanticipated problem</u> that occurs during the conduct of this study and that meets **at least** the first two criteria listed in section 8.2 must be reported to the UNC IRB using the IRB's web-based reporting system.

6.2. Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of study participants treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

7. STATISTICAL CONSIDERATIONS

7.1. Study Design/Study Endpoints

This prospective single instituted study will enroll about 30 patients that are scheduled to have screening breast MRI study to have the investigational MR sequences in the same study schedule adding no more than 12 minutes scanning time. The study ends when enough number of patients collected and analyzed.

7.2. Sample Size and Accrual

Our objective is to approximate the reliability for the 3D MR Fingerprinting method, which can be quantified by the Intraclass Correlation Coefficients (ICC). Given the previous preliminary experience of Dr. Yong Chen using 3T MRI in Case Western Hospital, the ICC for T1 and T2 MRF are 0.82 and 0.875, respectively, with 12 healthy pre-menopausal volunteers scanned twice within 7-15 days. Suppose we choose 30 normal subjects and select 2 breast tissue locations for both left and right breasts for each subject to obtain 120 breast tissue images. For each breast tissue image we have two measurements using the MRF. For T1, our hypothesis test is ***H0: ICC= 0.82 vs. H1: ICC<0.82***, and the power will be 0.858 with significance level α =0.05 according to [17, 18], if the true

ICC=0.72; the power will be 0.935 with significance level α =0.05, if the true ICC=0.70. For T2 image, if we test H0: ***ICC= 0.875 vs. H1: ICC<0.875***, the power will be 0.969 with significance level α =0.05, if the true ICC=0.775; the power will be 0.873 with significance level α =0.05, if the true ICC=0.80; the power will be 0.749 with significance level α =0.05, if the true ICC=0.815. Therefore, we propose 30 normal control subjects with measurements twice, to measure the reliability of the 3D MRF technology. The measurement will be evaluated for both before and after contrast enhancement.

7.3. Data Analysis Plans

We will calculate the inter-subject and intra-subject variability and estimate the ICC and its confidence interval for both the T1 and T2 values of normal breast tissue between the two MRF sequences at pre-contrast phase, and the post contrast delayed phase, respectively, to establish the parameter stability between scan times. We will also estimate the T1, T2 value change from pre to post contrast enhancement phases to establish the baseline value of normal breast parenchyma at pre and post contrast enhancement phases. We will compare the results with previous literature [19] and use independent two sample t-test to check if significant difference between MRF and with results in previous literature does not exist.

8. STUDY MANAGEMENT

8.1. Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRBapproved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.2. Registration Procedures

Study participants will be registered into OnCore®, a web based clinical research platform by one of the Study Coordinators.

8.3. Data Management and Monitoring/Auditing

Image datasets will be stored on a secure server in the Biomedical Research Imaging Center with patient identifiers removed. De-identified copies of these may be stored temporarily on password-protected computers or portable hard drives for use in data analysis. Quantitative data extracted from the images and results of data analysis will be maintained on a secure server. All data will be archived on a password-protected computer in the office of the PI and backed up with a RAID system. Datasets will be maintained for at least five years from the close of the study.

8.4. Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.4.1. Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, an IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

8.4.2. Single Subject Exceptions

8.4.3. Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy. Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study team using the IRB's web-based reporting system.

8.5. Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

8.6. Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the

study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.7. Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study participants. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

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