Official Title:	Pilot study for Prone Breath Hold Technique to Decrease Cardiac and Pulmonary Doses in Women Receiving Left Breast Radiotherapy
NCT number:	NCT02379988
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	Protocol version 08/17/2015 – IRB approved 08/25/2015

Pilot Study For Prone Breath Hold Technique to Decrease Cardiac and Pulmonary Doses in Women Receiving Left Breast Radiotherapy

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Protocol Version and Date
Version 4, 8/17/2015

Investigator Agreement Version 4 8/17/2015

I have read, understand and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.

I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

_____ _____

Signature Date (MM/DD/YY)

Victor Gonzalez, MD
Name of Principal Investigator

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1. INTRODUCTION

1.1 Phase:
This is a pilot study to determine whether the addition of inspiratory hold (breath holding) can decrease the radiation dose that the heart receives for patients being treated for left sided breast cancer.

1.2 Indication:
Utilizing prone radiation therapy along with inspiratory hold to reduce the radiation dose to the heart and lungs.

1.3 Endpoints:

Primary
The primary endpoint is the feasibility of the breath-hold technique for women treated with radiation for left-sided breast cancer in the prone position.

Secondary
The secondary endpoint is to evaluate the changes in mean dose to the heart and lungs with prone breath hold. Other secondary endpoints include heart volume receiving 20 Gy, maximum dose to left ventricle/LAD artery and relative volumes of lung receiving 20 Gy.

1.4 Patient population:
Eligible subjects must be able to understand and sign the study specific subject consent form. They must be patients of Dr. Gonzalez and ≥18 years of age. Eligible subjects must also have node-negative left breast cancer, invasive or DCIS breast cancer and have had a prior lumpectomy and deemed appropriate for treatment in the prone position by the treating physician. They must be able to tolerate breath-hold in the prone position.

2. STUDY DESIGN

2.1 Phase: This is a Pilot Study

2.2 Number of centers: One
This study will be performed by The University of Arizona Medical Center (UAMC) Radiation Oncology Department at both the University Campus Hospital and Orange Grove Clinic.

2.3 Number of subjects: Approximately 15

2.4 Subject participation time period:
Subjects will be enrolled in the study for 15 months, including screening time, treatment time, and follow-up at one year post radiation therapy.

Subjects enrolled in this study are undergoing treatment at UAMC Main Campus or Orange Grove Clinic as part of standard of care for the treatment of breast

cancer. Typical Radiation treatment schedule is between four and six weeks in length with treatments administered Monday through Friday.

SCHEMA

See Section 9.3

3. OBJECTIVES

3.1 Primary:
The primary endpoint is the feasibility of the breath-hold technique for women treated with radiation for left-sided breast cancer in the prone position.

3.2 Secondary:
To determine whether cardiac dose and lung dose can be reduced in women receiving prone breast radiotherapy when inspiratory gating is added. To evaluate the changes in mean dose to the heart and lungs with prone breath hold. Other secondary endpoints include heart volume receiving 20 Gy, maximum dose to left ventricle/LAD artery and relative volumes of lung receiving 20 Gy.

4. BACKGROUND and RATIONALE

4.1 **Disease**

4.2 There are currently estimated to be more than 2.8 million breast cancer survivors alive in the United States. Among these women, approximately 50% have received radiotherapy as part of their primary treatment. Adjuvant radiotherapy following lumpectomy improves both local control as well as overall survival. As such, whole breast radiotherapy following lumpectomy is the standard of care for women under 70. With advances in treatment, cure rates for early stage breast cancer now frequently exceed 95%. For these reasons, interventions aimed at reducing the long-term risks of radiotherapy are critical in this population as more survivors are living longer.

Late cardiac toxicity from breast radiotherapy is well documented. Early randomized studies from the 1970s and 80s comparing lumpectomy alone to lumpectomy plus radiotherapy demonstrated improved cause specific survival with the addition of radiotherapy. However, this cancer-specific survival benefit was negated by an increased risk of cardiac mortality 10-20 years following radiotherapy (Clarke et al 2005). While technical improvements in radiotherapy have dramatically reduced the risk of cardiac injury, recent studies have continued to demonstrate a small but significant increased risk of cardiovascular events following breast radiotherapy. Darby et al recently demonstrated that the risk of cardiac events following radiotherapy is directly proportional to the mean heart dose (Darby et al 2013). Thus, methods for reducing cardiac dose will be anticipated to reduce the long term risk of cardiac disease.

The two methods most frequently used to reduce cardiac dose during breast radiotherapy are prone positioning on a breast-board and inspiratory gated breath-

hold treatment. Lymberis et al prospectively studied 100 patients with CT simulation scans for RT planning in the prone and supine setups. It was found that prone position decreased the volume of lung within the radiation field in all patients and for left sided breast cancers 87% of patients had a decrease in irradiated volume of the heart. Formenti et al published their abstract of 200 patients with left-sided breast cancer who underwent radiotherapy treatment planning in both the prone and supine position. Radiation treatment plans for each position were compared specifically looking at doses to heart and lung volumes. Their results showed that prone positioning was associated with a 91.1% reduction in lung radiation dose and 85.7% reduction of in-field heart volume. A critique of the prone position is that due to gravity not only does the breast tissue fall away from the chest wall but the heart falls anteriorly towards the chest wall.

Remouchamp et al evaluated moderate deep-inspiration breath hold (DIBH) in external beam radiation treatment of left sided breast cancer. The treatment plans from the breath hold and free breathing CTs were compared showing a mean decrease of 3.6% of heart volume that received 30Gy. This would translate into a 1.5% decrease in the rate of heart normal tissue complication probability (NTCP). However, the absolute lung volume seeing higher doses of radiation is increased with DIBH but relative lung percentages receiving significant radiation doses may be improved. A retrospective study (Nissen et al 2013) reviewed 144 left-sided breast cancer patients treated with DIBH and 83 left-sided patients treated free breathing. The heart mean dose was decreased from 5.2 to 2.7Gy.

While both methods have independently been demonstrated to reduce cardiac dose and pulmonary dose, the combination of the two have not been reported. This study seeks to evaluate whether cardiac dose and pulmonary dose can further be reduced in women receiving prone breast radiotherapy with the addition of inspiratory gating. We anticipate that prone breath hold can further reduce radiation doses to these organs at risk, and potentially reduce the risk of late cardiovascular and pulmonary complications from breast radiotherapy.

If this study shows feasibility and potential for lowering cardiac and pulmonary dose for patients treated in the prone position with the addition of breath-hold then a larger randomized trial looking at optimal patient characteristics for this combined technique, further examining dose reductions using this experimental technique versus standard of care, and possible late toxicities, including cardiovascular and pulmonary, can be considered in the future.

4.2 Investigational Product:

Not applicable

4.3 Pre-clinical Experience

Not applicable

4.4 Clinical Experience

The two methods most frequently used to reduce cardiac dose during breast radiotherapy are prone positioning on a breast-board and inspiratory gated breath-hold treatment. Lymberis et al prospectively studied 100 patients with CT simulation scans for RT planning in the prone and supine setups. It was found that prone position decreased the volume of lung within the radiation field in all patients and for left sided breast cancers 87% of patients had a decrease in irradiated volume of the heart. Formenti et al published their abstract of 200 patients with left-sided breast cancer who underwent radiotherapy treatment planning in both the prone and supine position. Radiation treatment plans for each position were compared specifically looking at doses to heart and lung volumes. Their results showed that prone positioning was associated with a 91.1% reduction in lung radiation dose and 85.7% reduction of in-field heart volume. A critique of the prone position is that due to gravity not only does the breast tissue fall away from the chest wall but the heart falls anteriorly towards the chest wall.

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5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product (IP)
Not Applicable

5.2 Investigational Product Supply
Not Applicable

5.3 Investigational Product Accountability
Not Applicable

5.4 Storage
Not Applicable

5.5 Preparation
Not Applicable

5.6 Handling
Not Applicable

6. SUBJECT ELIGIBILITY

Investigators will maintain an electronic subject log in the UACC OnCore and RedCao system of all potential (i.e. consented) study subjects, which will include as applicable (demographics, informed consent, eligibility, treatment assignment, on treatment, off treatment, follow up and off study dates).

6.1 Inclusion Criteria

1. Patients of Dr. Gonzalez
2. ≥18 years of age
3. Node-negative left breast cancer
4. Invasive or DCIS breast cancer
5. Prior lumpectomy
6. Deemed appropriate for treatment in the prone position by the treating physician
7. Able to tolerate prone position and breath hold during CT simulation
8. Patient must be English speaking.

6.2 Exclusion Criteria

1. <18 years of age
2. Patients requiring treatment in supine position

6.3 Enrollment

The source of subjects is the patient population at the Banner – University Medical Center Tucson/Arizona Cancer Center. Patients who are scheduled as part of their routine care to consult with the radiation oncologist for treatment of left sided breast cancer will be provided with information regarding this study. See attached list for our website, newsletter and Front Desk Poster.

Subjects will be consented at an already scheduled appointment with the radiation oncologist. This could be either at their initial consult visit or prior to their CT simulation appointment. Subjects will have the opportunity to take their time in making a decision, and will be encouraged to take the Informed Consent Form home and discuss it with whomever they would like. The treating physician will explain to the subjects the risks and benefits. They will be informed that their participation is voluntary, and lack of participation will not affect the subject's relationship with the treating staff or our facility. Subjects will be consented by either the PI, Co –PI, or the Research Staff of the Radiation Oncology department. Subjects will also be made aware that should they consent, they can withdraw their consent at any time. When new information becomes available, it

will be given to the patient as soon as possible, either at their next visit, or if that is more than 30 days away, by phone call. Once an approved revised consent form is submitted and approved by the IRB, the subject will be asked to sign the new consent and the subject will be notified of the change to the consent form. The AZCC Verification of Consent form will be completed at the time the subject is consented. This form includes information pertaining to who is present at consenting, that the consent form was reviewed with the subject, the subject understood the consent form, and the date and the time of the consent. Also documented will be the version of the Subject Consent form and the HIPAA form. Only English speaking patients will be enrolled.

7. STUDY PLAN

7.1 Treatment Regimen

Subjects will be recruited by Dr. Gonzalez and Dr. Goyal (or covering physician) at their standard of care appointment prior to the radiation planning appointment. Patients will be asked by Dr. Gonzalez and Dr. Goyal (or covering physician) if they are interested in participating in the study. If they are, a member of the research staff will review the study with the patient and complete the consent process. Subjects will be enrolled prior to their radiation therapy panning simulation (CT simulation).

During the radiation planning appointment, patients undergo CT scans used to plan the radiation doses and delivery. The number of images taken during the CT simulation is the same is if they were not treated on this research study. A CT scan will be performed in the prone position using coached voluntary inspiratory breath-holding using the RPM visual feedback system. Prone breath hold will be conducted using a monitor in the headrest of the prone breastboard that the subject will watch. This monitor allows the subjects to see their respiratory cycle which is a sinusoidal curve. Therapists coach the patient to hold their breath for approximately 15 seconds in order to maintain inspiration within a threshold bar set by the simulation therapists that is seen via the patient monitor. The purpose of the breath hold technique is to allow for optimal heart positioning for this study. This is the same method used for breath hold in the supine position which is considered standard of care. The reason this study is unique is because it is using the combination of prone positioning and inspiratory gated breath hold versus individually.

After the subject completes the radiation planning simulation, the physician will generate two radiation treatment plans: one for the free-breathing scan (standard of care) and one for the breath-hold scan (using inspiratory gating). For each plan, the heart, left ventricle/LAD artery and lungs will be contoured on each CT scan with radiation fields placed on both CT scans to dosimetrically determine heart, left ventricle/LAD artery and lung radiation doses and coverage of the affected breast. The doses to the heart, left ventricle/LAD artery and lungs will be compared to determine the plan with the lower cardiac and lung doses.

At the discretion of the treating physician, the plan with the lower cardiac and lung doses will be used to treat the subject. Inspiratory breath hold will only be used if it results in lower cardiac and lung doses. If the free breathing plan shows

lower cardiac and lung doses, the patient will be treated per standard of care (prone without inspiratory breath hold). If the plan involves inspiratory breath hold, the subject will be notified by the research staff prior to the first day of treatment. Reasoning for treating a patient prone only versus prone and breath-hold will be documented by the treating physician. If the plan with inspiratory breath hold resulted in the lower cardiac and lung dose, inspiratory gating will be performed during each daily treatment. Treatment with breath hold adds approximately 5 minutes to the overall setup and treatment time of each daily treatment. During daily radiation, prone breath hold will be conducted using a monitor below the prone headrest that the patient will watch. This monitor allows the patient to see their respiratory cycle and indicates the amount of inhalation that would be required (threshold bar represented as a blue box) in order to allow for treatment that is representative each day of their initial simulation CT scan. This monitor allows the subjects to see their respiratory cycle which is somewhat of a sinusoidal curve. Therapists coach the patient to hold their breath for approximately 15 seconds in order to maintain inspiration within a threshold bar (blue box) set by the simulation therapists that is seen via the patient monitor. During treatment, the radiation beam is only active when the patient breath hold is within the threshold bar on the monitor. The radiation treatment machine is set to turn off when the breath hold is outside of this threshold bar (blue box).

The physician will complete an evaluation form (RTOG CF form attached) regarding cardiac co-morbidities. The form will be completed at baseline (radiation planning session) and at 6 months post RT, and then at 1 year. This will not require any additional time for the subject and will be based on the information gathered by the physician at the standard of care appointment.

In addition to the intervention, data from the subjects medical record will also be collected (please see attached data collection sheet). Details regarding the subject's treatment, imaging studies, medical history and follow up visits will be collected. The research staff has access to the medical record as part of their position with UA/UAMC.

7.2 Pre-medications:
Not Applicable

7.3 Rescue medications:
Not Applicable

7.4 Excluded medications:
Not Applicable

8. REQUIREMENTS FOR TREATMENT

8.1 Standard dose/treatment
Not applicable

8.2 Dose/treatment modification
Not applicable

8.3 Investigational Product Dose Delay
Not Applicable

8.4 Definition of a Dose Limiting Toxicity (DLT)
Not Applicable

9. STUDY PROCEDURES (the actual procedures need to be entered below and/or in a study schema/calendar – see my note in section # 26)

9.1 Screening
Potential subjects will enter the screening period of the study after completely executing a study specific informed consent form.

9.2 Registration/Randomization
Once this study is approved by all internal regulatory agencies to enroll subjects, study enrollment will begin. Subjects will be entered into the study. Subjects will be identified by their initials (First, Middle if available, Last) and a study number. Study numbers will begin with GO-B-001and continue sequentially.
The subject CT Simulation will be scheduled.

9.3 On Intervention: Subjects will undergo the standard of care CT simulation, which includes an additional breath hold CT. Inspiratory gated breath-hold will be used. Two radiation plans will be generated: one for the CT scan performed free breathing, and one for the scan performed with inspiratory gated breath hold. The cardiac and lung doses will be determined. At the discretion of the treating physician, the plan with the lower cardiac and lung dose may be used to treat the patient.

9.4 End of Intervention: The intervention will be considered complete at the time the patient's treatment plan has been generated.

9.5 Follow up
Subjects will be seen for one 30 day [±10 days] follow-up visit after the end of RT then at 6 months (± 30 days) and then at one year (± 30 days) from the end of radiation therapy. These visits are part of RT standard of care. During each of these visits, patients will be asked about any cardiac or pulmonary changes, including any cardiac or pulmonary symptoms [i.e. shortness of breath, rapid heart beat, chest pain, and whether or not they have had any cardiac or pulmonary testing (i.e. ECG, echo, muga or PFTs)].

9.6 Early intervention termination
Not Applicable

9.7 Off study

Subjects will be considered off study after completing their one year (+/- 30 days) post RT follow-up visit. Subjects will also be considered off study if they chose to voluntarily withdraw from the study. They will be asked to be seen for a final end

of study follow-up that would include the same procedures as the follow-up appt. described in Section 9.5.

10. PHARMACOKINETIC STUDIES

Not applicable

11. DATA AND SAFETY MONITORING PLAN

11.1 Identification of the DSMB obligated for oversight responsibilities:

The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial.

11.2 Identification of the entity obligated for routine monitoring duties:

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

11.3 Monitoring progress and data review process:

Routine monitoring of subject data will be conducted at least annually.
The first routine monitoring visit will include at a minimum:

- Informed consent – 50% of cases enrolled;
- Subject eligibility - 10% of cases, up to two subjects;
- Data review - 10% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. A query/finding form or an electronic record will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form, or will be notified of the electronic record for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms *[other forms, depending on study]* should be completed via the institution database or other acceptable data

formats. Trials using paper CRFs will have the data entered with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents and test article will be conducted at least annually.

11.4 **Process to implement study closure when significant risks or benefits are identified:**

There are no plans for early study closure for this study, since the intervention used will actually reduce the side effects patients experience.

11.5 **Description of adverse events and reporting procedures:**

ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a casual relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UMC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or 4.0 and will address:

- Grade
- Relationship to study drug(not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and DSMB Coordinator. All serious adverse events, regardless of attribution, and any deaths will be reported within 5 days of notification of the event to the University of Arizona Human Subjects Protection Program.

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every six months. The DSMB Coordinator will review the SAE reporting process to confirm reporting requirements are met.

11.6 **Plan for assuring data accuracy and protocol compliance:**
Routine study activity and safety information will be reported to the DSMB on an annual basis, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least annually.

. **Identification of the sponsor or funding agency, as applicable:**
The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study.
A copy of this correspondence will also be forwarded to the DSMB and the SRC.

11.7 Process to implement study closure when significant risks or benefits are identified:
Not applicable.

12. ADDITIONAL SAFETY REPORTING

Serious adverse events will be reported to the Data Safety Monitoring Board as well as the institutional IRB within 24 hours of notification of the event to the PI.

Serious adverse events will be reported using the FDA MedWatch form to inform the DSMB, and using the F224 (Reportable Local New Information that is Potentially Problematic) form to inform the IRB.

13. QUALITY ASSURANCE MEASURES

Not applicable

14. RECIST CRITERIA

Not Applicable

15. REMOVAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational intervention.

The investigator or designee must document the change in status of the subject's participation in the study and as applicable, the level of follow up that is agreed to by the subject (i.e. agrees to follow up exams, adverse event review, phone contact, but not to further treatment and/or procedures).

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

16. STASTISITICAL CONSIDERATIONS

Statistical analysis will be performed in collaboration with Dr. Denise Roe, the Director of the University of Arizona Cancer Center Biometry Shared Service.

The primary endpoint of the study is the feasibility of the breath-hold technique for women treated with radiation for left-sided breast cancer in the prone position. Although it is expected that the number of women who are unable to master the breath-hold technique will be small, the proportion of women who cannot master the technique will be estimated with the appropriate exact 95% confidence interval.

The secondary endpoint is to evaluate the changes in the mean dose to the heart and lungs with prone breath hold. Each woman enrolled in the study will have two radiation plans generated in the prone position: one for the free-breathing scan and one for the breath-hold scan. The mean difference between the dosimetrically determined heart and lung radiation doses will be computed with the associated 95% confidence interval. A paired t test will be used to assess

whether the mean difference is statistically significant. The other secondary endpoints will be analyzed in a similar fashion.

Ten women will give 80% statistical power to detect a difference of 1 standard deviation unit in the mean dose between the two conditions. Note that since paired data will be generated, the number of women required is less than if two independent samples of women were to be used. Additionally, the percentage of women in which adding the breath-hold results in a lower cardiac and lung dose will be estimated with standard error of 16% or less. The estimated mean difference (and its standard error) will be used to generate the sample size required for a larger study to statically assess the benefit of adding the breath-hold in reducing the cardiac and lung radiation dose.

17. ANALYSIS

17.1 Safety Analysis
Not applicable

17.2 Efficacy Analysis
Efficacy analysis will be conducted at the completion of the study.

17.3 Interim Analysis
Not applicable

18. REGULATORY OBLIGATIONS

18.1 Informed consent
Before a subject's participation in the clinical study, the investigators or identified designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures, investigational product, intervention or device are administered or initiated.

18.2 Institutional Review Board
A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the institution before recruitment of subjects into the study.

The investigator is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments; except changes to eliminate an immediate hazard to study subjects, and changes to the informed consent document from the IRB prior to implementation.

The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other serious adverse event reports occurring at or received from participating centers as applicable for multi-center trials following the IRB policies and procedures.

19. ADMINISTRATIVE PROCEDURES

19.1 Investigator responsibilities
The PI will conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

19.2 Data and Safety Monitoring Board protocol review
Initial DSMB protocol review will be conducted prior to SRC and IRB submissions.

Any protocol revision or amendment that includes a potential change to any section of data and safety monitoring plan must be reviewed and approved by the DSMB prior to the protocol amendment submission to the IRB.

19.3 Multicenter Trials
Not Applicable

19.3.1 UACC DSMB and QA/QC Monitoring
The UACC QA/QC Program will be responsible for routine monitoring of local study data for the coordinating center.

19.3.2 Alternate DSMB Oversight
Not Applicable

20. SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

21. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of appropriately qualified persons to whom he has delegated study duties. All persons authorized to make entries and/or

corrections on case report forms (CRF) will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

22. DATA

Applicable data as specified as required in the protocol will be reported/submitted in the CRF. Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. CRFs will be completed via the OnCore system and RedCap. which is currently being used by many UMC departments for their study data bases.

Additional procedures and assessments may be performed as the institution's standard of care; however these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to a serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational intervention.

23. PROTOCOL DEVIATIONS

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

Approvals or waivers for protocol deviations will be obtained from the investigator prior to occurring, except changes to eliminate an immediate hazard to study subjects. If immediate verbal approval is obtained, it will be documented by the research staff obtaining the approval and followed by a written protocol deviation form per the site standard operating procedures. The investigator will sign the Protocol Deviation (Waiver) Approval Form or other similar document. The original will be filed in the regulatory binder and a copy will be placed in the subject's research file.

24. KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS

Not Applicable

25. COMMON TOXICITY CRITERIA

CTCAE version 4.0

26. STUDY SCHEDULE

See Section 9

27. GLOSSARY:

Not Applicable

28. DEFINITIONS:

Not Applicable

29. REFERENCES

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30. APPENDIX

30.1 CF Form
30.2 Data Collection Form