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Intra-patient Comparison of Active Breathing Coordinator-based vs VisionRT-based Deep Inspiration Breath-hold for Left-chest Wall Irradiation, a Pilot Study for Breast Cancer

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Intra-patient comparison of Active Breathing Coordinator-based *vs* VisionRT-based deep inspiration breath-hold for left-chest wall irradiation, A Pilot Study for Breast Cancer

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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.

Amendment # 4

STU 052015-047
Intra-patient comparison of Active Breathing Coordinator-based *vs* VisionRT-based deep inspiration breath-hold for left-chest wall irradiation, A Pilot Study for Breast Cancer

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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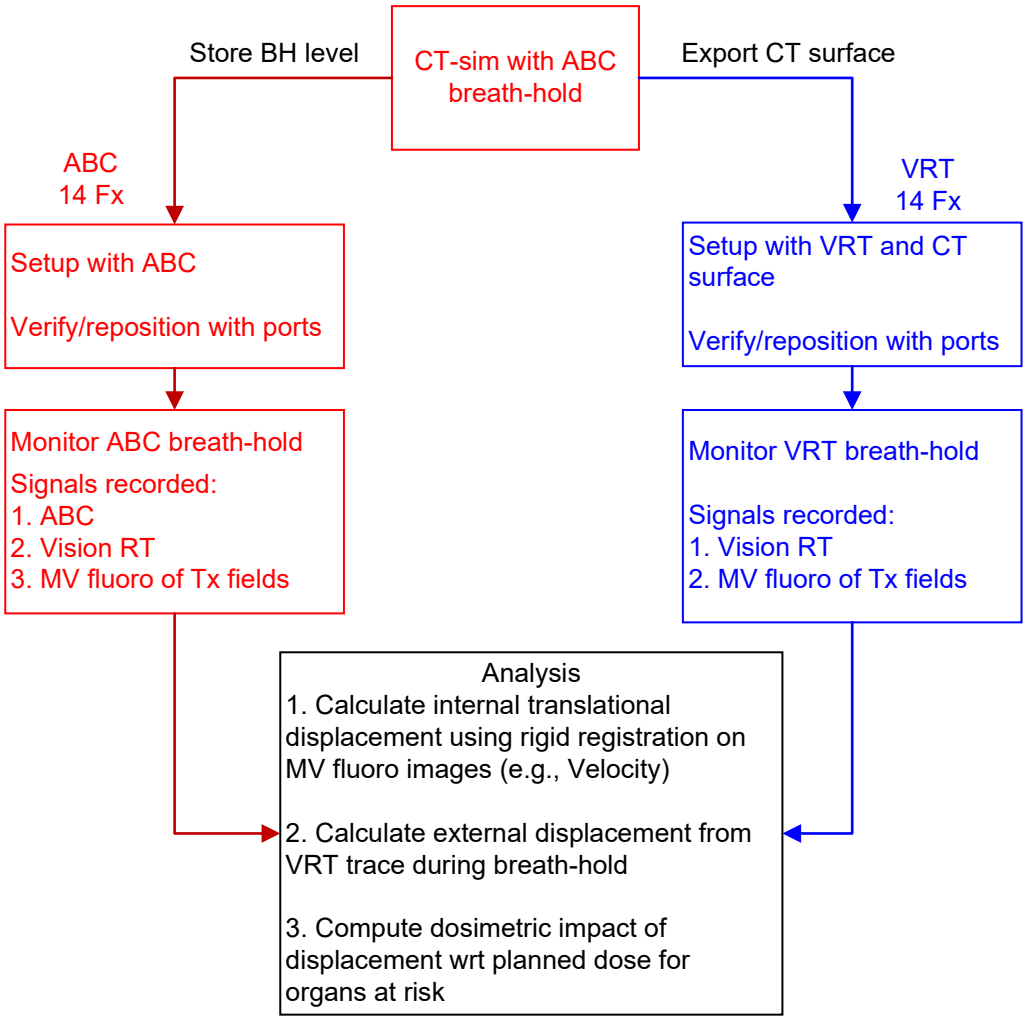
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ABC	Active Breathing Coordinator
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
BH	Breath Hold
BUN	Blood Urea Nitrogen
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MV	Mega Voltage
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
VRT	Vision RT

STUDY SCHEMA



STUDY SUMMARY

Title	Intra-patient comparison of Active Breathing Coordinator-based *vs* VisionRT-based deep inspiration breath-hold for left-chest wall irradiation
Short Title	Intra-patient study of ABC vs VisionRT DIBH for left-chest wall irradiation
Protocol Number	**STU 052015-047**
Phase	Pilot
Methodology	Female patients treated with radiation for left-sided breast malignancy will undergo alternate fractions of ABC-assisted and VisionRT-assisted DIBH. Residual motion during breath-hold will be quantitatively assessed using MV fluoroscopy from the treatment beam itself (i.e., no additional radiation dose). The dosimetric impact of residual motion on organs at risk (heart and lung) will be assessed by applying rigid and/or deformable displacements to the planning CT images, computing the 3D dose map and comparing with the original planned dose map.
Study Duration	One year
Study Center(s)	Single-center UTSW
Objectives	1. To quantify residual motion in ABC-assisted vs VRT-assisted DIBH 2. To quantify the dosimetric impact of residual motion on the heart and lung.
Number of Subjects	10
Diagnosis and Main Inclusion Criteria	Women with left sided breast malignancy undergoing post-mastectomy radiation
Study Product(s), Dose, Route, Regimen	Left-sided chest wall irradiation; 1.8 Gy x 28 fractions.
Duration of administration	28 days
Statistical Methodology	As this is a pilot study, we will accrue 10 patients and use descriptive statistics.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Whole breast radiation after lumpectomy is the current standard of care for early stage breast cancer. Whole breast radiation is typically delivered with two-four tangential radiation beams in order to avoid en-face radiation to the lungs and heart (Fig. 1).

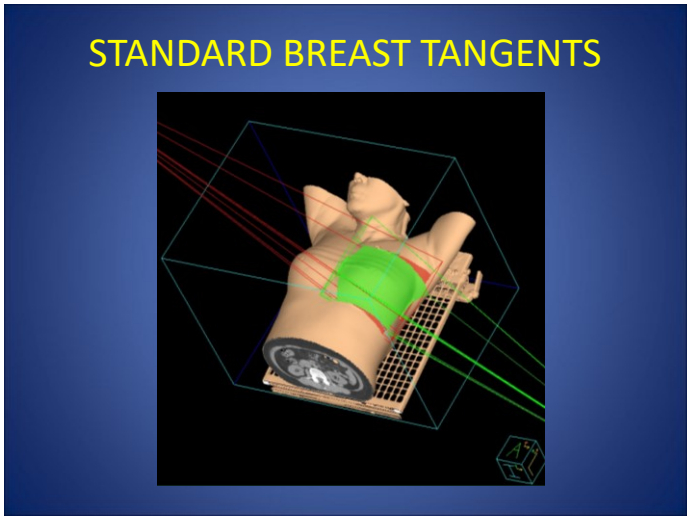


Figure 1. Standard breast tangents for left-sided breast irradiation

Despite this technique, for left sided breast cancers, the heart and ipsilateral lung still receive minimal doses of radiation. Some studies have alluded to long-term survival for breast cancer survivors being compromised by late cardiac toxicity such as coronary artery disease.[1, 2] Darby et al, reported that cardiac risk increases linearly with mean heart dose by 7.4%/Gray without a threshold.[1]

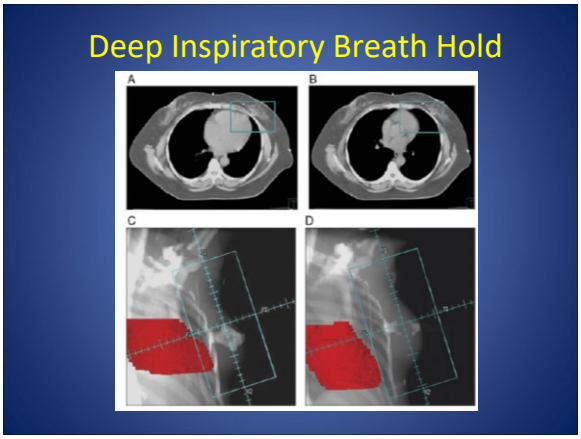


Figure 2. Positions of the heart in the absence (a,c) and presence (b,d) of DIBH.

Deep inspiratory breath hold (DIBH) techniques have been developed to help minimize cardiac and lung dose. As a patient takes a deep breath, the lungs fill with air, causing the heart to be displaced posteriorly and inferiorly outside of the radiation tangential beams. This movement increases the distance between the heart and chest wall. With this distance in place, the radiation tangential beams can target the breast or chest wall with significantly less cardiac irradiation. Figure 2 demonstrates the position of the heart during free breathing in Figures 2a and c and how it is displaced out of the radiation portal in Figures 2b and d with a DIBH.

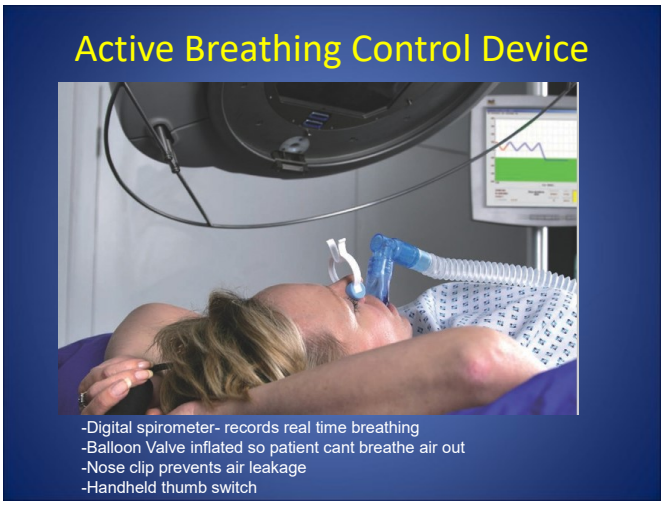


Figure 3. ABC-assisted deep inspiration breath-hold

There are several ways to assist in DIBH during radiation treatments. One of the more common ways is by using a commercially available system Active Breathing Coordinator (ABC; Elekta, Crawley, UK) device. The ABC system has a digital spirometer that records real time breathing. When the patient inspires to a preset DIBH level, a balloon valve is inflated so as to prevent the patient from breathing out and thereby maintain a consistent chest wall expansion with each DIBH. A nose clip prevents air leakage. The therapist monitors the respiratory cycle and DIBH on the screen during the radiation delivery. When the patient depresses a handheld thumb switch, treatment is stopped and valve opens so breathing can resume normally again. Dosimetric advantages of cardiac sparing using DIBH ABC technique have been shown.[3, 4]

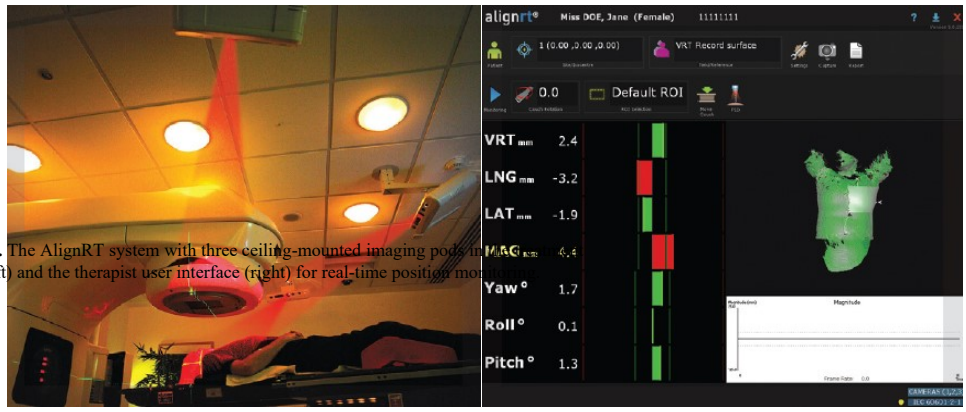


Figure 4. The AlignRT system with three ceiling-mounted imaging pods in the treatment room (left) and the therapist user interface (right) for real-time position mo

A more recent, competing technology for implementing the DIBH technique is real-time surface photogrammetry using the AlignRT system (Vision RT Ltd., London, UK), shown in Figure 4. The patient is CT simulated in the DIBH position. The 3D DIBH external surface rendering at the time of CT scan serves as a baseline. In the treatment room, a speckled optical pattern in the visible red range is projected on the patient's thoraco-abdominal surface by each of three ceiling-mounted imaging pods. Once the patient has matched the pre-determined DIBH position (with 2 mm accuracy), the radiation beam is enabled to be turned on for treatment. The optical pattern is imaged by optical cameras (two per pod) at ~25 Hz. The user selects a region-of-interest (ROI) on the surface and the software calculates and displays the real-time position in six degrees (3 translations and 3 rotations) in real-time (Figure 4 right panel). Since visible light is used for the position monitoring, there is no additional (non-therapeutic) ionizing radiation delivered to the patient.

Several studies have pointed out potential drawbacks of the ABC system. E.g., even though the patient's tidal volume remains consistent with ABC, different breathing maneuvers (abdominal versus thoracic breathing) can cause for variations in breath-hold.[5] They reported that for the same vital capacity, abdominal and thoracic breathing led to an average difference of chest wall expansion of 1.9 cm. Remouchamps et al. also showed that that overshoot can occur with ABC device where the patient can inhale a larger air volume than the pre-determined set limit.[3, 6] More recently, Mittauer et al. showed through using an optical surface-tracking system to monitor ABC assisted DIBH, that large positional variations can occur in some patients due to their different breath hold techniques, causing increases in mean heart and coronary artery dose.[7]

In contrast, the VisionRT system has several potential advantages. First, it monitors patient (surface) position which is a more relevant surrogate for internal motion than the tidal volume (e.g., the tidal volume can remain the same even if the patient shifts slightly on the couch). Thus VRT can monitor residual motion during the breath-hold. Second, from a clinical standpoint, the VRT system

- requires no patient training during sim or Tx
- takes approximately half the time for treatment
- Is much more cost effective, as patient tubing needs to be replaced daily for ABC

The one potential advantage of ABC over VRT is that the former system performs an assisted breath-hold (i.e., the patient is actively impeded from inhale/exhale) while the VRT system depends entirely on patient compliance.

The purpose of this study is to perform an intra-patient comparison of ABC vs VisionRT for DIBH in left-sided chest wall radiotherapy. The primary goals are to record the presence and magnitude of residual motion during DIBH and determine the clinical impact of motion in terms of changes in heart and lung dose with respect to that calculated in the treatment plan.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To quantify residual motion during deep inspiratory breath-hold using ABC and Vision RT during left post-mastectomy chest wall radiotherapy

2.1.2 To determine clinical and dosimetric impact of residual motion, on heart and lung dose

2.2 Secondary Objectives

2.2.1 To compare time of simulation and daily treatment for DIBH with both ABC and Vision RT

2.2.2 To evaluate DIBH reproducibility of both ABC and vision RT DIBH

2.3 Endpoints

To quantify residual motion during DIBH using ABC and VRT, MV fluoro images of treatment fields will be acquired during daily radiation fractions. These motions will be plotted out, to quantify amount of chest wall motion during daily treatments. The mean, and median value of motion obtained for VRT DIBH and ABC DIBH will then be translated to axial CT images using deformable registration in Velocity, and dosimetric impact of residual motion on critical organs such as the heart and lung will then be quantified.

Minutes of daily radiation setup and treatment delivery will be recorded for all daily radiation fractions. Mean and median setup and treatment delivery times for ABC versus VRT will then be compared.

The DIBH levels will be recorded daily (on both ABC and VRT days) using the VisionRT system and the inter-fraction reproducibility of the DIBH level will be calculated for ABC and VisionRT.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Women with diagnosis of breast malignancy
3.1.2 Women whom requires left chest wall post-mastectomy radiation with or without bolus

3.1.3 Age ≥ 18 years.

3.1.4 Performance status ECOG </=3

3.1.5 Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, and during radiation therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.5.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.6 Ability to understand and the willingness to sign a written informed consent.
3.1.7 Patient must be able to maintain a 30 second breath hold.
3.1.8 Conventional chest wall radiation delivery dose of 50.4 Gy/ 28 fractions with or without a boost (boost will not be evaluated for endpoints)

3.2 Exclusion Criteria

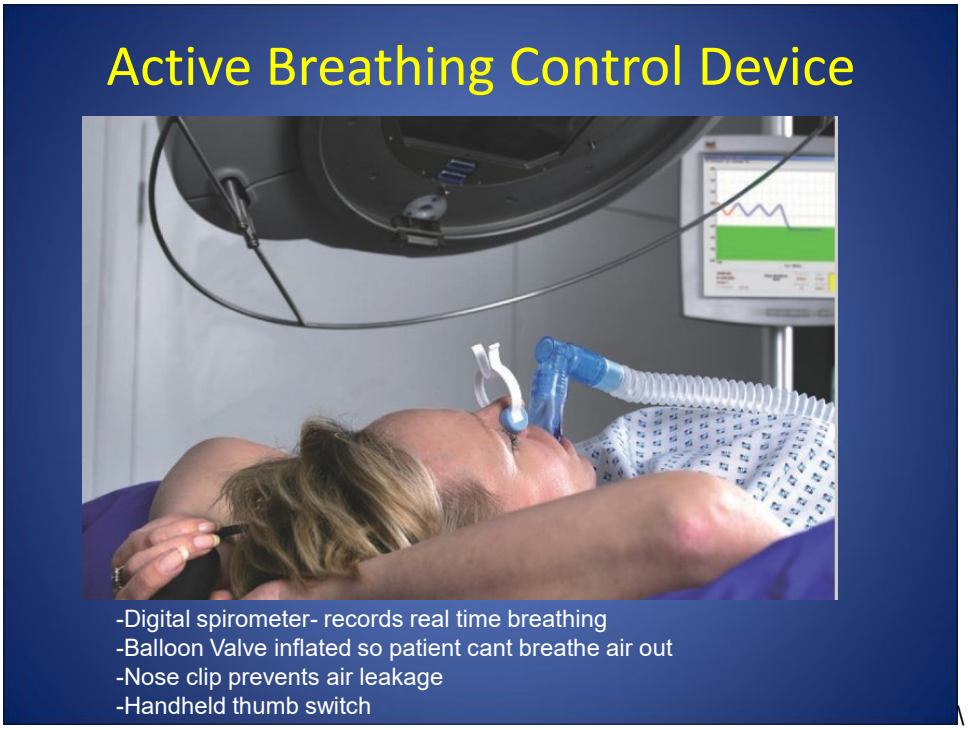
3.2.1 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social **situations that would limit compliance with study requirements.**

3.2.2 Subjects must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Simulation: Patients will be simulated on the breast board supine with arms abducted and externally rotated. A vac lok bag will be made to immobilize patient arms. Patients head will be turned to the right side to avoid facial irradiation. Wire markers will be placed mid-sternum, 2 cm inferior to the inframammary fold, mid-axillary line, and at the level of the clavicular head. A wire marker will be placed over the lumpectomy scar. Patient will then have a CT scan in the treatment position with normal free breathing. ABC machine will then be set up. Nasal clip will be placed on nose to prevent air leakage from nasal cavity. Digital spirometer tubing will be placed in patient's mouth to record real time breathing on computer monitor. Patient given hand held thumb switch in order to control breathing. ***Care must be taken to ensure tubing is not over left chest, as same CT images will be used to acquire VRT surface rendering.*** Patient instructed to take in a deep breath, while maintaining scapula on table and not arching back. CT scan acquired with ABC assisted breath hold.



After CT simulation, both free breathing and ABC DIBH images transferred to pinnacle treatment planning software. Exported DICOM DIBH surface will then be used to acquire baseline VRT surface rendering.

Free breathing and breath hold CT simulation images will be visually compared to assure there is an advantage to proceed with breath hold technique. 3-D Treatment planning on breath hold scan will proceed. Patients will then be treated daily with breath hold technique, using only the ABC device every other day. The VRT software will be used on a daily basis in conjunction with the ABC device, and solely on days when ABC is not used. Results will then be analyzed by interpreting the MV images and after determining amount of respiratory movement during ABC and VRT, retrospectively re-planning the breast plans.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Expected toxicities are those that we would normally consent patients for breast radiation. As we are not modifying the dose or treatment volume from standard breast radiation we will not have dose modifications.
Potential breast radiotherapy toxicities include: dermatitis, fatigue, hyperpigmentation, brachial plexopathy, radiation pneumonitis, shrinkage of the breast, coronary artery disease, pericarditis, rib damage or fracture.

4.3 Duration of Therapy

End of protocol therapy will be the last day of radiation. Other exceptions may apply:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator".

4.4 Duration of Follow Up

- No follow-up required for this study after radiation completed. F/up per standard of care for malignancy per treating radiation oncologist

4.5 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. The PI will be notified and a Note to File will be written for Removal of Subjects from study, when taken off study treatment, withdrawn at their own request or at the discretion of the investigator (detailed reasons listed in Section 5.5). The subject should be followed-up per protocol.

4.6 Subject Replacement

If a subject is withdrawn from the study prior to completing radiation therapy without experiencing a SAE prior to withdrawal, an additional subject may be added.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 60 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 ***Informed Consent***

5.1.2 ***Medical history***

Complete medical and surgical history

5.1.3 ***Demographics***

Age

5.1.4 ***Review subject eligibility criteria***

5.1.5 ***Physical exam including vital signs, height and weight***

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.6 ***Performance status***

Performance status evaluated prior to study entry.

5.1.7 ***Adverse event assessment***

See section 6 for Adverse Event monitoring and reporting.

5.2 Procedures During Treatment

5.2.1 Prior to Radiation Treatment Cycle

- Physical exam, vital signs
- Consent
- Eligibility/ineligibility criteria

5.2.2 CT simulation

- CT Simulation scan in free breathing
- CT simulation scan with DIBH and ABC machine- must ensure tubing from ABC not over chest wall so skin rendering is able to be reproduced
- Preparation of vac lock bag, coaching for breath hold should not be included in timing
- Planning and contouring-
- Structures that should be contoured are lumpectomy cavity, heart, left anterior descending artery, lungs, and ipsilateral breast tissue
- Simulation and treatment may be performed with the patient in the supine position only
- Patients should be optimally positioned with alpha cradle casts, breast boards, or wing boards and/ or other methods of immobilization at the discretion of the treating physician.
- A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV) and planning target volumes (PTV
- Radio-opaque markers should be placed on external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) The mastectomy incision 2) The outline of the palpable chest wall tissue circumferentially at least from 2 o'clock to 10 o'clock 3) The superior border of the chest wall tissue at 12 o'clock based on palpation. Additional markers to define the borders of "clinical" tangent fields (e.g. based on the palpable chest wall tissue and boney landmarks) are often helpful.
- The CT should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of ≤ 0.5 cm should be employed.
- External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.
- CT simulation will likely be around 1 hour in length one time

Treatment Planning/Target Volumes

The definitions for the CTV, PTV and normal structures used in this protocol generally conform to the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer (http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx) and the 1993 ICRU report #50: Prescribing, Recording and Reporting Photon Beam Therapy.
The plans generated using forward-planning methods or segmental techniques such as "field-in-field" to meet dose-volume constraints are considered as 3DCRT
plans. These forward-planned or segmental treatment techniques are those

intended to mainly improve the uniformity of the dose distribution, but not to produce steep dose gradients to protect critical structures (e.g., heart or lung). 3D-CRT should be used for planning.

Chestwall CTV: Includes the Mastectomy Scar CTV, and takes into account the radiopaque markers placed at CT identifying clinical extent of chestwall, surgical changes visualized by CT, and consensus definitions of anatomical borders of chestwall from the RTOG Breast Cancer Atlas http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.
The Chestwall CTV is limited by the skin anteriorly and should not extend deeper than the ribs so that it excludes the lung and heart. Depending on the location of the Mastectomy Scar CTV, it should exclude the sternum medially and the axilla deep to anterior surface of the pectoralis major muscle laterally. In general, the chestwall CTV should not cross midline.
Expanders, implants or autologous tissue present for reconstruction will be included in the Chestwall CTV. The degree of expander expansion present is per the treating physician's discretion. The expander should remain at the same expansion through the course of treatment that is present for the CT simulation.

Chestwall PTV: Chestwall CTV + 7 mm 3D expansion (excludes heart and does not cross midline).

Chestwall PTV Eval: As a part of the Chestwall PTV often extends outside the patient, the Chestwall PTV is then copied to a Chestwall PTV Eval which is edited. This Chestwall PTV Eval is limited anteriorly to exclude the part outside the patient and the first 3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis) and posteriorly is limited to no deeper than the posterior rib surface and excludes lung and heart. In general, the Chestwall CTV should not cross midline. This Chestwall PTV Eval is the structure used for DVH constraints and analysis and not for beam aperture generation.

Ipsilateral lung. This may be contoured with auto-segmentation with manual verification.

Contralateral lung. This may be contoured with auto-segmentation with manual verification

Heart: This is to be contoured on all cases- not just the left sided cases. The heart should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice thereafter to its inferior
most extent near the diaphragm. The following structures if identifiable should be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.
Left Anterior Descending Artery: The left anterior descending artery (LAD), including the small segment of left coronary artery before bifurcation, was contoured, with a 3-mm diameter, from its origin, continued between the left ventricle and right ventricle in the interventricular groove, and to the inferior border of
the heart.

Thyroid: The thyroid is easily visible on a non-contrast CT due to its preferential absorption of Iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in

shape and often do not converge anteriorly at mid-line. All “bright” thyroid tissue should be contoured.

Treatment Planning: Treatment Planning CT-based planning with tissue inhomogeneity correction is required.
The following critical organs dosimetric parameters will be recorded for dosimetric comparison:

- Suggested Dose Parameters- at Discretion of treating Radiation Oncologist
-≥ 95% of the Chestwall PTV Eval will receive ≥ 95% (47.5 Gy) of the chestwall dose of 50 Gy
-</= 5% of the whole heart should receive ≥ 25 Gy for left-sided breast cancers
-V20 total lung <30%

5.2.3 **Daily Treatment**

- First 14 fractions to be set up with ABC for DIBH or Vision RT (patient will be randomized as to which starts first)
- Last 14 fractions to be set up with Vision RT for DIBH or ABC (patient will be randomized as to which starts second)
- Each daily fraction should be timed and recorded from moment patient lays on treatment table to last radiation beam treated (treatments will be timed and recorded per institutional standard).
-days when portals taken will be recorded to account for longer set up times
-Weekly Port films will be taken with both ABC and vision RT (this should increase time on treatment table by roughly 10 minutes, once weekly and is considered standard of care)
- ABC DIBH and VRT DIBH signals of chest wall motion will both be recorded during radiation treatment using Mega Voltage (MV) fluoroscopy (this should not increase treatment time as MV radiation fluoroscopy being used is from actual radiation treatment)

-

5.2.4 **Post-Radiation Analysis**

-calculate internal translational displacement using rigid registration on MV fluoro images (ie; Velocity)
-calculate external displacement from VRT trace during DIBH
-after displacement recorded, dosimetric plans will be rerun taking into account displacement (deformable registration), and to determine impact of mean displacement on critical organs such as lung and heart
-Determine the variance of DIBH with ABC and VRT to determine reproducibility
-Compare mean, median and range for average time of daily radiation set up and delivery for ABC and VR

5.3 Follow-up Procedures

- No follow-up required for this study after radiation completed. F/up per standard of care for malignancy per treating radiation oncologist

5.4 Time and Events Table [When appropriate, this may be referenced and included in the appendices rather than within the body of the protocol. Consider landscape format when necessary to include all of the appropriate procedures and tests.]

	Pre-study	Daily during radiation	Weekly during radiation
Assessment			
Informed Consent	X		
History and PE	X		
Performance Status	X		
Port films			X
Timing daily radiation set up and delivery		X	
MV flouro of treatment fields		X	

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up.

5.6 Randomization

In order to minimize technology-specific bias in this pilot study, ten patients will be randomly assigned to two groups of five patients each. The probability of being assigned to each group is 0.5. Randomization log will be created. Five patients in group 1 will be administered 14 fractions with ABC-assisted DIBH, followed by 14 fractions with VRT-

assisted DIBH. Five patients in group 2 will be administered 14 fractions with VRT-assisted DIBH, followed by 14 fractions with ABC-assisted DIBH.

6.0 ADVERSE EVENTS

6.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

6.1.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through treatment, until the last day, will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

6.1.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- 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;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

6.2 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur *to the end of the acute adverse events reporting period as defined in section 6.1*.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

6.2.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Written reports to: Sarmistha Sen 2280 Inwood Rd Dallas, TX 75390 UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects

(UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

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7.0 STATISTICAL CONSIDERATIONS

Statistical aspects of this study will be developed in consultation with Dr. Chul Ahn from the Department of Clinical Sciences. As this is a pilot study, we will accrue 10 patients and use descriptive statistics to characterize the extent of motion during DIBH and its dosimetric impact in terms of increased dose to the heart and lung. The findings from these studies will be used to inform the sample size for a future larger scale (Phase II) study.

7.1 Study Design/Study Endpoints

A single-center prospective pilot study will be conducted according to the schema outlined at the beginning of this document. Informed consent will be obtained from ten post-mastectomy, left-sided breast cancer patients, each to be treated with 50.4 Gy/ 28 fx. In order to minimize technology-specific bias, the patients will be divided into two groups of five each. Group 1 will be administered 14 fractions with ABC-assisted DIBH, followed by 14 fractions with VRT-assisted DIBH. Group 2 will be administered 14 fractions with VRT-assisted DIBH, followed by 14 fractions with ABC-assisted DIBH. (Both ABC and VRT are FDA-approved for clinical use and are used in our clinic as standard-of-care.)

In each case, the residual motion during DIBH-assisted dose delivery will be recorded via MV fluoroscopy of the exiting beam using an electronic portal imaging device (EPID). Note that this procedure does not involve the administration of any additional non-therapeutic ionizing radiation to the patient (other than the prescribed dose).

7.2 Sample Size and Accrual

As this is a pilot study, we will accrue 10 patients and use descriptive statistics to characterize the extent of motion during DIBH and its dosimetric impact in terms of increased dose to the heart and lung. The findings from these studies will be used to inform the sample size for a future larger scale (Phase II) study.

7.3 Data Analyses Plans

Individual frames from each MV fluoroscopic series will be imported into Velocity (a clinically available medical image processing software) and a rigid registration will be performed between successive frames in order to quantify the residual motion during a DIBH. The mean, and median value of motion obtained for VRT DIBH and ABC DIBH will then be used to translate axial CT images in Velocity and the originally planned beam arrangement will be used to recalculate the treatment plan and compute the dose to the displaced anatomy. In this manner, the dosimetric impact of residual motion on critical organs such as the heart and lung will be quantified.

8.0 STUDY MANAGEMENT

8.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

8.2 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

Toxicity and dose escalation reviews will be annually. The reviews will be documented by written report saved in the study folder.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to

ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

8.3 Adherence to the Protocol

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

8.3.1 **Exceptions** (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

8.3.2 **Emergency Deviations:** include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

8.3.3 **Major Deviations** (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

8.3.4 **Minor Deviations:** include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

8.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. 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 the IRB for approval prior to implementation.

8.5 Record Retention

Study documentation includesdata correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, Note to Files when a patient is removed from the study, 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 the study investigator retain all study documentation pertaining to the conduct of a clinical trial. 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.

8.6 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 patients. 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.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected. . Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data.

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