STU 022017-075

VisionRT-based Deep Inspiration Breath-hold (DIBH) Respiratory Motion Management Strategy, A Pilot Study for Thoracic and Abdominal Tumors Stereotactic Body Radiotherapy

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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.

Version #4

STU 022017-075

VisionRT-based Deep Inspiration Breath-hold (DIBH) Respiratory Motion Management Strategy, A Pilot Study for Thoracic and Abdominal Tumors Stereotactic Body Radiotherapy

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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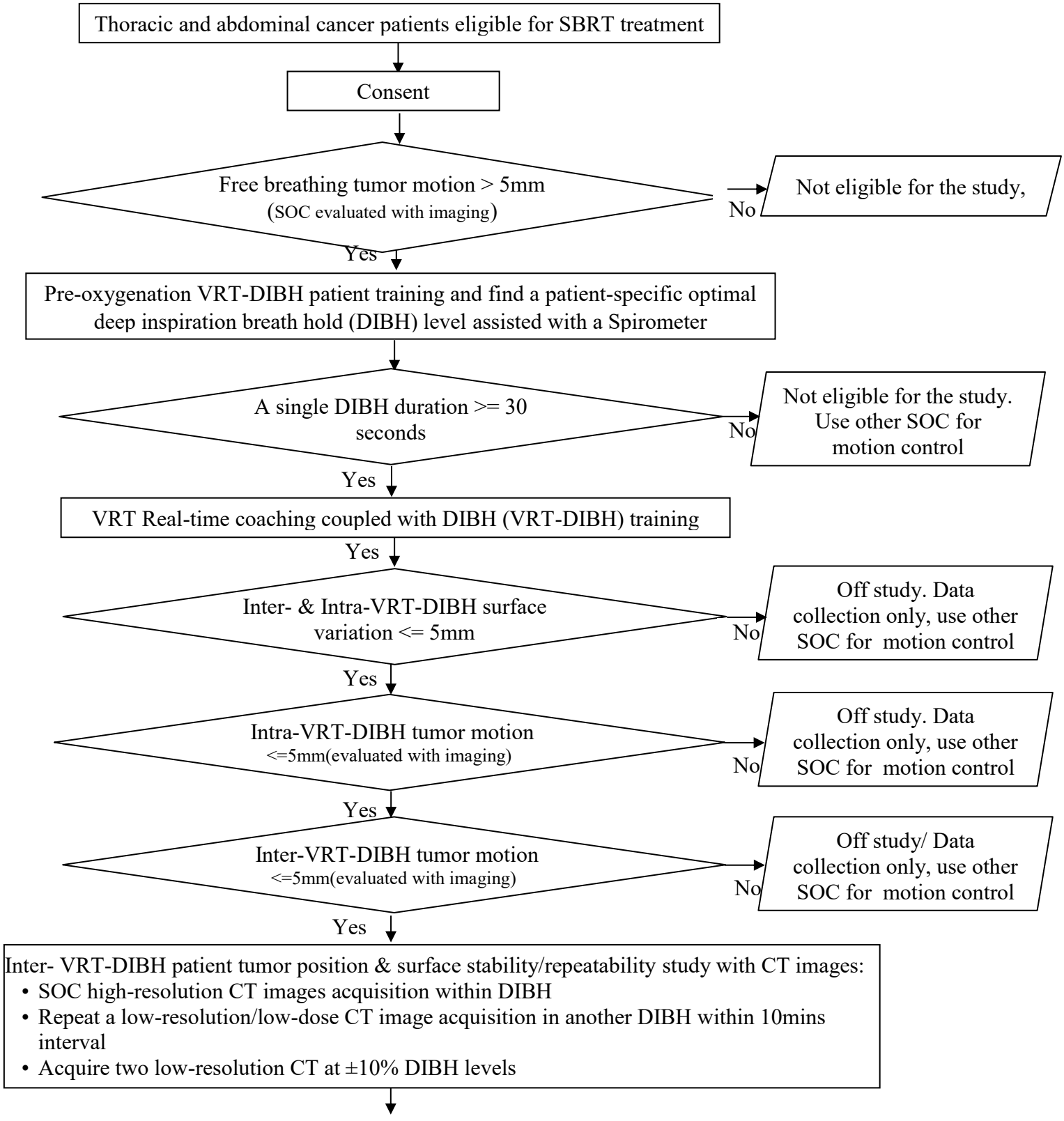
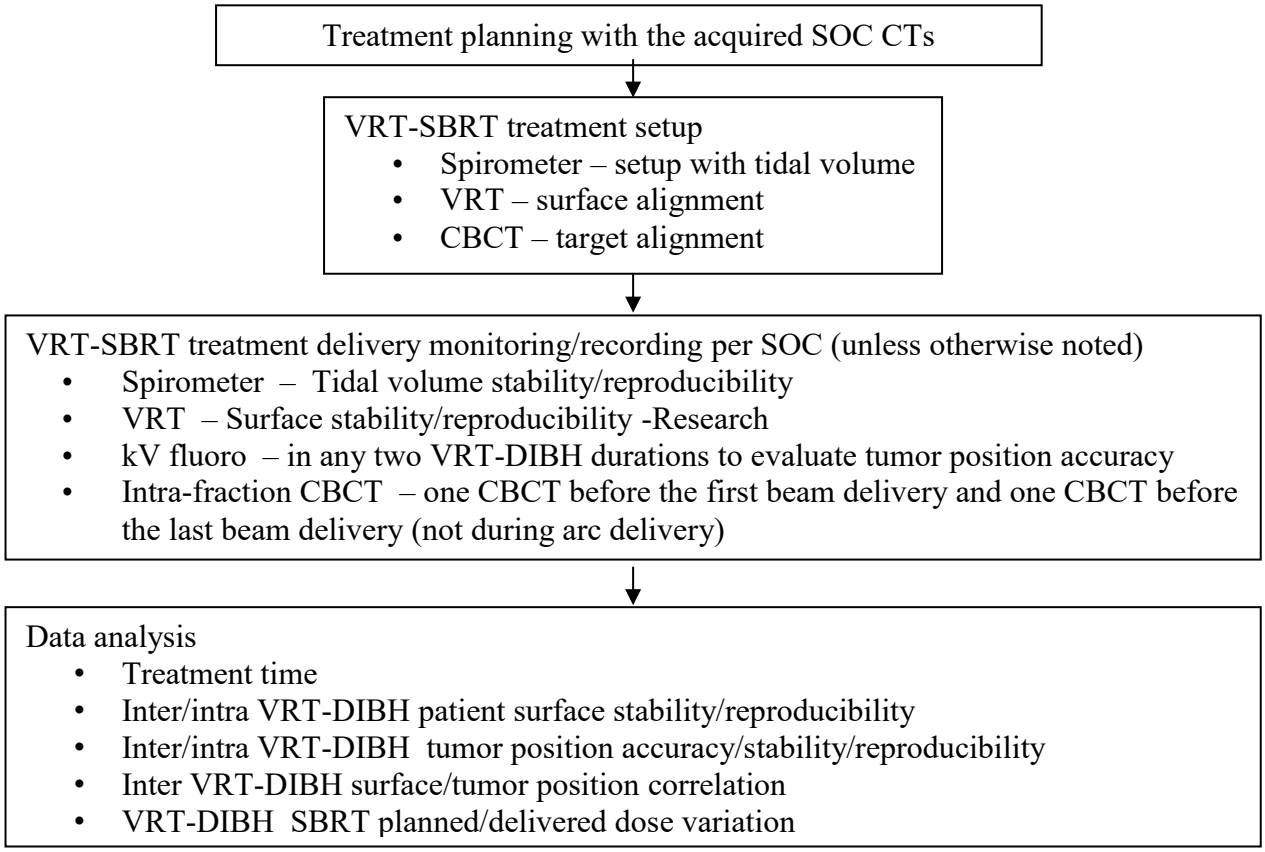
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ABC	Active Breathing Coordinator
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
BH	Breath Hold
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MV	Mega Voltage
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
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
SOC	Standard of Care
VRT	Vision RT
VRT-DIBH	VRT-assisted DIBH

STUDY SCHEMA




Treatment planning with the acquired SOC CTs
VRT-SBRT treatment setup
• Spirometer – setup with tidal volume
• VRT – surface alignment
• CBCT – target alignment
VRT-SBRT treatment delivery monitoring/recording per SOC (unless otherwise noted)
• Spirometer – Tidal volume stability/reproducibility
• VRT – Surface stability/reproducibility -Research
• kV fluoro – in any two VRT-DIBH durations to evaluate tumor position accuracy
• Intra-fraction CBCT – one CBCT before the first beam delivery and one CBCT before the last beam delivery (not during arc delivery)
Data analysis
• Treatment time
• Inter/intra VRT-DIBH patient surface stability/reproducibility
• Inter/intra VRT-DIBH tumor position accuracy/stability/reproducibility
• Inter VRT-DIBH surface/tumor position correlation
• VRT-DIBH SBRT planned/delivered dose variation

STUDY SUMMARY

Title	VisionRT-based Deep Inspiration Breath-hold (DIBH) Respiratory Motion Management Strategy, A Pilot Study for Thoracic and Abdominal Tumors Stereotactic Body Radiotherapy
Short Title	VRT-DIBH for Thoracic and Abdominal Cancer SBRT
Protocol Number	STU 022017-075
Phase	Pilot
Methodology	Prospective study with retrospective data analysis
Study Duration	2 year
Study Center(s)	Single-center
Objectives	To prove the feasibility of using VRT-DIBH for thoracic and abdominal tumors SBRT
Number of Subjects	10
Diagnosis and Main Inclusion Criteria	• Patients with tumors in thorax and abdomen • Patients are eligible for SBRT
Study Product(s), Dose, Route, Regimen	No therapeutic intervention – per SOC
Duration of administration	Per SOC
Statistical Methodology	Descriptive statistics will be computed to investigate the feasibility of the trial.

1.0 BACKGROUND AND RATIONALE

1.1 Background

Respiratory motion affects all tumor sites in the thorax and abdomen. The disease of most prevalence and relevance for motion-management needed radiotherapy are lung and liver cancer. Lung cancer is the leading cause of cancer-related mortality in the United States. During 2016, an estimated 224,390 new cases of lung cancer are diagnosed, representing 13% of all cancer patients[1], and an estimated 158,080 deaths of lung cancer were expected[1]. The five-year survival rate for all stages combined is 17.7%, lower than many other leading cancer sites, such as the colon (64.4%), breast (89.7%) and prostate (98.9%)[2]. Liver cancer is the 10th most common cancer. In 2016, an estimated 39,230 adults (28,410 men and 10,820 women) in the United States will be diagnosed with primary liver cancer[1]. The 5-year survival rate of liver cancer is 17%[2].

Stereotactic body radiotherapy (SBRT) is a therapeutic paradigm developed in the mid 1990's. It administers very high, biological potent doses in few fractions (1 - 5 fractions) using unique beam arrangements and special immobilization equipment. It has demonstrated excellent local control in patients with inoperable non-small cell lung cancer (NSCLC)[3] and liver cancer[4] .

Respiratory motion causes significant geometric and dosimetric uncertainties in lung and upper abdomen cancer radiotherapy treatment simulation, planning, and delivery[5]. These uncertainties are particularly large in SBRT, potentially leading to significant collateral toxicity[6-8] when using large beam apertures or, conversely, potential marginal miss with very small apertures. Researchers and clinicians have been investigating respiratory motion-management techniques for over a decade.[9, 10] A variety of motion management strategies have been explored and implemented for clinical use, including motion-encompassing methods [e.g. 4D CT and ITV (internal target volume) approach], abdominal compression techniques to decrease motion amplitude, breath-holding methods, respiratory-gating techniques, and real-time tumor-tracking methods. All of these techniques aim to mitigate dosimetric uncertainties induced by respiratory motion by either restricting or compensating for motion.

1.2 DIBH and Active Breathing Coordinator (ABC)

Among various respiratory motion management techniques, deep-inspiration breath-hold (DIBH) technique has been developed and applied in lung and liver SBRT.[11, 12] DIBH has shown advantages for treating thoracic and abdominal tumors because it can significantly reduce respiratory tumor motion and changes internal anatomy in way that often protects critical normal tissues.

There are several ways to assist DIBH during radiation treatments. One common way 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 signals 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.[13, 14] Currently, UTSW lung and liver SBRT and left breast conventional irradiation are used ABC assisted DIBH (ABC-DIBH) for respiratory motion management.

Several studies have pointed out potential drawbacks of the ABC system. For example, 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.[15] 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.[13, 16] 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[17] and concluded that optical tracking system is a valuable tool for ABC-assisted DIBH.

1.3 VRT and VRT-DIBH

A more recent competing technology for implementing the DIBH technique is real-time surface photogrammetry using the AlignRT system (Vision RT Ltd., London, UK). AlignRT system use non-ionization near infrared light to track patient surface motion. The system has one projector projecting near infrared optical pattern on patient surface. 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. Once the patient has matched the pre-determined DIBH position (within threshold accuracy), the radiation beam is enabled to be turned on for treatment.

Currently, VRT-DIBH has already applied to left breast radiotherapy to spare lung and heart. Compared to ABC-DIBH, VRT-DIBH has several potential advantages:

1. VRT monitors patient (surface) position in addition to DIBH signal, while ABC only check the tidal volume, which can remain the same even if the patient shifts slightly on the couch;
2. VRT is more cost effective, as patient tubing needs to be replaced daily for ABC;
3. VRT potentially has advantage on patient compliance, as with ABC breath is forced impeded while with VRT breath-hold is voluntary.

In this study, we renovate the established DIBH motion management strategy by adopting AlignRT system. The purpose of this study is to develop, validate, and prove the feasibility of VRT-DIBH technique for lung and liver SBRT.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To investigate the feasibility of applying VRT-DIBH to lung/liver cancer SBRT

2.2 Secondary Objectives

2.2.1 To determine planning target volume margin by investigating tumor residual motion in VRT-DIBH

2.2.2 To determine VRT surface monitoring threshold by investigating inter/intra VRT-DIBH patient surface stability/reproducibility/sensitivity

2.3 Exploratory Objectives

2.3.1 To quantify SBRT dose variation between planned and delivered with VRT-DIBH technique.

2.3.2 Treatment time

2.4 Endpoints

2.4.1 VRT-DIBH feasibility

2.4.2 To determine target margin in VRT-DIBH lung/liver SBRT

2.4.3 To determine threshold used for surface monitoring in VRT-DIBH assisted lung/liver SBRT

3.0 PATIENT 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 Patients must be willing and capable to provide informed consent to participate in the protocol.

3.1.2 Patient with presumed pulmonary function capable of holding breath for at least 30 seconds – later to be confirmed.

3.1.3 All men, as well as women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, and until study imaging is complete. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.6.1 A female of child-bearing potential is any woman (regardless of sexual orientation, marital status, 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).

3.1.4 Patients must be compliant to all required pretreatment evaluations (section 5.1)

3.2 Exclusion Criteria

3.2.1 Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus

3.2.2 Patients are not compliant to all required pretreatment evaluations (section 5.1).

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Patient recruit on this treatment protocol will go through training-screening sessions:

1. Patient will go through a tumor motion evaluation session. Since we would like to test the effectiveness of our proposed motion management strategy, we would like to recruit patient with tumor motion in one direction is larger than 5 mm. Tumor motion in free-breathing mode will be evaluated under imaging study..
2. Patient will go through a pre-oxygenation training-screening session. Research studies[18, 19] already shown that pre-oxygenation can effectively prolong breath-holds in patients with cancer. In this study we will combine patient training, screening, and pre-oxygenation to prolong patient breath-hold duration in radiotherapy procedure. Patient will be asked to breathing oxygen-enhanced air through a facial mask and take deep inspiration breath hold. We will use spirometer to find the maximum deep inspiration breath level and set a comfortable/optimal breath hold level ~75% of the maximum deep inspiration. Only patient can have single DIBH duration >= 30 seconds will be eligible for the study.
3. Patient will go through a real-time coaching training session assisted by DIBH technique. After being trained, patient will go through motion assessment section. Patient will be set on treatment couch with chest exposed which allows cameras catch patient body surface information. Spirometer will be used to assist DIBH setup. Optical camera system will be used to acquire patient chest/abdomen surface. During the surface image acquisition, imaging will be used to acquire tumor position or diaphragm position. The surface images and tumor positions acquired in single DIBH durations will be used to quantify intra-DIBH patient surface and tumor position stability. The surface images and tumor positions acquired across several DIBH durations will be used to quantify inter-DIBH patient surface and tumor position repeatability. The intermittent time between DIBH durations can be varied between 1-10 minutes.
4. Only patient with inter/intra-DIBH tumor position variation <=5 mm and inter/intra-DIBH surface level variation <= 5 mm will be move on for this VRT-DIBH protocol study. Otherwise, patients will be off study and treated per standard of care.

DIBH qualified patient will experience one high-resolution CT scan as SOC and additional lower dose CT scans to further investigate inter-DIBH patient surface and tumor position stability and repeatability.

1. Spirometer will be used to select DIBH level and monitor DIBH status during CT simulation. One SOC high-resolution CT will be acquired in single DIBH duration. Within 10 minute, a low-resolution/low-dose CT image in single DIBH duration will be acquired. This study is to quantify inter-DIBH tumor position and patient surface repeatability.
2. Patient will then be scanned using a lower dose CT protocol with DIBH level set at ±10% deviated from the selected DIBH level. This study is to find the correlation between DIBH level and tumor position /chest-abdomen surface level.

The SOC DIBH CT scan will be transferred to Eclipse treatment planning system for treatment planning. Tidal volume measured by spirometer and DIBH surface from CT image will be used as a reference surface for patient treatment initial setup. CBCT will be acquired before each fractional treatment for the patient alignment before beam delivery.

During the treatment delivery, patient will perform DIBH while AlignRT system monitors patient surface. As a pilot study, we will also use spirometer to monitor patient breath-hold tidal volume, and imaging acquired in any two DIBH periods to quantify inter- and intra- DIBH tumor position variation. Following our SBRT treatment protocol, patient will get CBCT scan before the last beam delivery. We will follow the same protocol to acquire CBCT images. These CBCT images will be used to evaluate treatment dose variation to quantify treatment delivery accuracy.

4.2 Concomitant Medications/Treatments

Concomitant medications allowable as deemed appropriate by treating physicians.

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.

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. Notify the Principal Investigators, and document the reason for study removal and the date the subject was removed in the Case Report Form. 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 due to standard concerns for treatment side effects, an additional subject may be added. Notify the Principal Investigators, and document the reason for study replacement and the date the subject was removed in the Case Report Form.

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 Diagnosis*

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) for each protocol related visit.

5.1.6 *Adverse event assessment*

None

5.1.7 *Pregnancy test (for females of child bearing potential)*

See section 3.1.3 for definition. This is done prior to enrollment. Patients may refuse testing if they attest they are not pregnant.

5.1.8 *Breathing evaluation*

Treatment target motion, surface motion and breathing duration will be evaluated before SBRT (does not have to be done prior to registration). The following screening procedures will be pursued sequentially:

1. Free-breathing tumor motion evaluation: imaging will be acquired and physician will determine whether tumor motion > 5 mm.
2. For those patients with tumor motion > 5 mm, breath-holding duration will be evaluated. At this stage, patient will be positioned supine in a stable position. Patient will be asked to breathe oxygen-enhanced air and then take deep inspiration breath hold. Ask patient to repeat breath-holding 3 times and record breath-holding time. If patients can hold breath >= 30 seconds in all three times, patients will be eligible for the study.
3. Patient will be monitored by optical cameras to assess surface motion. Air tube will be setup to assist oxygen-enhanced air breathing. ***Care must be taken to ensure tubing is not over patient chest, as optical cameras will acquire surface images for motion evaluation.*** Patient will be instructed to conduct DIBH and optical cameras will monitor patient surface during breath hold. If surface motion > 5 mm during the breath hold, patient will not be qualitied for this trial. Another test is that we will instruct patient to repeat breath hold three times. If patient is able to repeat breath hold to the level of the first setting within 5 mm tolerance, patient will move on for the further study step.
4. DIBH tumor motion evaluation: after surface motion evaluation, DIBH tumor motion evaluation will be conducted under imaging one more time. Imaging will be acquired and physician will determine whether tumor motion <= 5 mm in one direction.

5.2 Procedures during Treatment

5.2.1 CT simulation

- CT Simulation scans at DIBH will be assisted by spirometer ---must ensure tubing from spirometer not over chest wall so skin rendering is able to be reproduced.
- CT simulation scan (full-length) will be acquired with at a single DIBH duration, starting at least 10 cm above the superior extent of tumor and continuing on every CT slice to at least 10 cm below the inferior extent of the tumor. DIBH signal will be monitored by spirometer. If there is no contraindication to contrast administration, patient will receive DIBH CT scans with contrast administration.
- CT acquisition should be done with gantry 0 degree with spacing ≤ 2 mm.
- Additional DIBH CT scans will be conducted using lower dose CT scan protocol. One at the same DIBH level and the other two will be ±10% deviated from DIBH breath level

- All images will be transferred to the treatment planning computers for tumor motion evaluation and planning.

5.2.2 Tumor motion evaluation and target volume delineation

On the acquired four different DIBH CTs, gross tumor volume (GTV) will be contoured by an appropriately trained physician. Tumor center point (center of mass) will be the identified and used for motion evaluation. Both inter- and intra- motion amplitude will be analyzed and margins will be estimated. The acquired high-resolution DIBH CT will be used as a primary image for planning. Physician will expand the GTV to PTV by adding proper size margins.

5.2.3 Critical organs delineation

SOC

5.2.4 Treatment planning

SOC

5.2.5 Daily treatment

- Patient will be positioned with vac lock bag in stereotactic body frame and setup with stereotactic coordinates recorded during simulation;
- Setup DIBH tidal volume use spirometer to reproduce simulated tidal volume;
- Initial setup patient position with AlignRT system using CT surface;
- Patient will receive a CBCT scan and align to simulated CT images;
- Right after CBCT alignment, AlignRT system will acquire a new surface image for treatment monitoring;
- Treatment delivery follows routine SBRT treatment, with one CBCT check before and one CBCT before last beam (not during treatment beam delivery).

5.2.8 Post-Radiation analysis

- Analyze recorded daily AlignRT treatment setup delta values
- Analyze recorded daily position shift using CBCT alignment
- Analyze recorded daily AlignRT treatment delta values, investigate surface stability and reproducibility
- Delineate tumor on recorded CBCT images and investigate the position error
- Project treatment beams on CBCT images and recalculate dose with CBCT images. Evaluate dose difference between the planned and the delivered.
- Treatment time analysis

5.3 Follow-up procedures

- No follow-up required for this study after radiation completed. Follow-up per standard of care for SBRT treatment per treating radiation oncologist.

5.4 Time and Events Table

	Pre-study	Treatment
Assessment		
Informed Consent	X	
History and PE[A]	X	X[C]
Pregnancy Test[B]	X	
CBCT scans		X

[A] include vital signs
[B] Recommended but patient may refuse if they attest they are not pregnant
[C] Only vital signs, once per week

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 from standard of care radiation treatment that the treating physician wants to stop the subject's continuation on the protocol

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

5.5.7 Subject becomes pregnant

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.

6.0 STATISTICAL CONSIDERATIONS

In this pilot study that aims to investigate the feasibility of applying VRT-DIBH to assist lung/liver cancer SBRT, we will recruit 10 patients. A sample size justification was not made since this is a pilot study to explore the feasibility of using VisionRT guided DIBH. Descriptive statistics will be computed to estimate the sample size needed for a future larger trial if the study results look promising. The trial is considered feasible and promising if 50% of enrolled patients can finish breath-holding SBRT.

6.1 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 10 thoracic or abdominal cancer patients, each to be treated with SBRT technique. In order to quantify tumor motion/surface stability and repeatability during VRT-DIBH, several CT images will be acquired during treatment simulation, as well as CBCT and VRT surface images during treatment delivery. The designed study aims to explore the geometry and dosimetry accuracy of VRT-DIBH in thoracic or abdominal cancer SBRT.

6.2 Sample Size and Accrual

As this is a pilot study, we will recruit 10 patients and use descriptive statistics to characterize tumor motion/surface stability & repeatability during VRT-DIBH and its dosimetric impact in terms of dose deviation to tumor and critical organs.

A sample size justification was not made since this is a pilot study. Descriptive statistics will be computed to estimate the sample size needed for a future larger trial if the study results look promising. We anticipate that the proposed trial will be completed in 2 years since at least 5 patients are expected to be recruited a year.

6.3 Data Analyses Plans

All recorded CBCT images will be used for tumor and critical organs geometry accuracy study by exporting to Velocity software. PTV and critical organs will be delineated. Tumor position accuracy will be evaluated. Further delivered dosimetric accuracy will be evaluated with through dose calculation on acquired CBCT images.

7.0 ADVERSE EVENTS

7.1 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 assessed 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.

[Inserted from Adverse Event Definitions and Reporting Section – Appendix II of the SCCC DSMC Plan]

7.1.1 Definitions

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, temporally 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 the last day of treatment 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

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- 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.

7.1.2 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.

7.2 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC

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 7.1.1.

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

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

SAEs and 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 occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the 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 or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. 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 or 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).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee 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 and 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: (Investigator/study team: Insert names, fax numbers, an addresses for required notifications)

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

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 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 HRPP within 5 working days of study team 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 study team 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/hrpp/quality-assurance/

7.3 Unblinding Procedures

Not applicable

7.4 Stopping Rules

Not applicable

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 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 must 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 subject 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 subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

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

8.3 Registration Procedures

All subjects must be registered with the Clinical Research Office, Department of Radiation Oncology, UTSW, before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Clinical research office Study Coordinator. To register a subject, call 214-633-1753 Monday through Friday, 9:00AM-5:00PM.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined

above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

8.4 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 according to the study specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

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 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 Quality Assurance Coordinator (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.

8.5 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.

8.5.1 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. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

8.5.2 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.

8.5.3 Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)

➢ **Reporting requirement***: Serious Noncompliance must be promptly reported tothe IRB within 5 working days of discovery..

8.5.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

➢ **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

8.5.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance

➢ Reporting requirement*: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first..

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

8.6 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.

8.7 Record Retention

Study documentation includes all Case Report Forms, 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 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.

8.8 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 and entered onto the Case Report Forms. 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. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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