STU 042018-100

Validation study of treating Arteriovenous Malformation with Stereotactic Radiosurgery using CT angiography for treatment planning

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Study Drug/Treatment: Radiation, Stereotactic Radiosurgery with Gamma Knife

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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/Version #: Version 3

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Principal Investigator (PI) Name: Robert Timmerman, M.D.

PI Signature: _____

Date: _____

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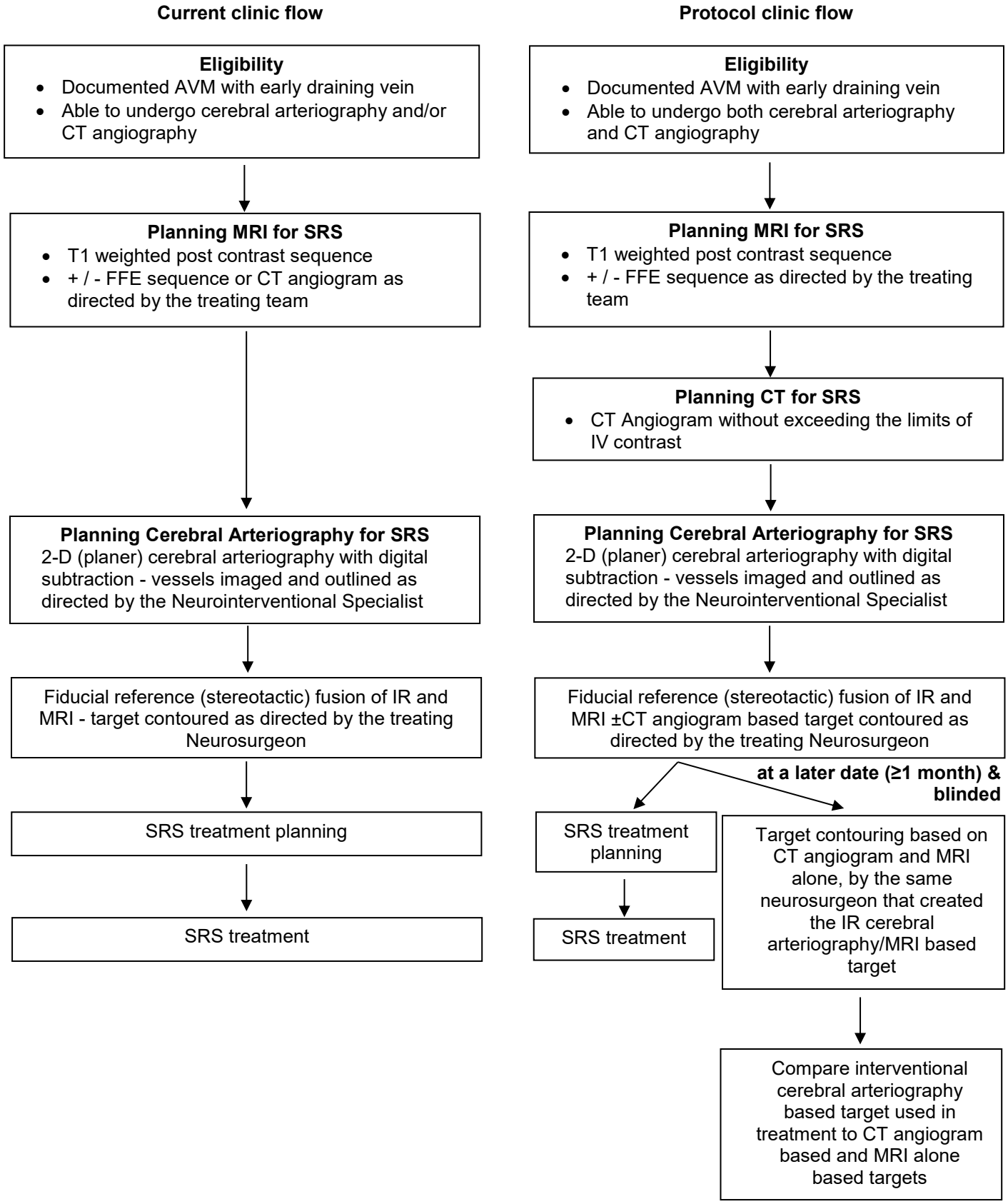
LIST OF ABBREVIATIONS

2-D	Two Dimensional
3-D	Three Dimensional
AE	Adverse Event
AVM	Arteriovenous malformation
CT	Computed Tomography
CTA	Computed Tomography Angiography
DC	Dice Coefficient
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FFE	Fast Field Echo
Gy	Gray
HD	Hausdorff distance
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HRQOL	Health-Related Quality of Life
ICH	International Conference of Harmonization
IRB	Institutional Review Board
IR	Interventional Radiology
IV	Intravenous
LINAC	Linear Accelerator
PE	Physical Exam
PTV	Planning Target Volume
Rx	Prescription
SAE	Serious Adverse Event
SRS	Stereotactic Radiosurgery
UTI	Urinary Tract Infection
UTSW	University of Texas Southwestern
V12	Volume of the brain that receives at least 12 Gray of radiation.

STUDY SCHEMA



STUDY SUMMARY

Title	Validation study of treating AVM with SRS using CT angiography for treatment planning
Short Title	SRS for AVM with CT angiography
Protocol Number	STU 042018-100
Phase	Feasibility
Methodology	Prospective enrollment and conduct open-label, retrospective analysis
Study Duration	2 years
Study Center(s)	Single-center
Objectives	Evaluate whether a treatment plan based on CT angiography can accurately and precisely identify the target nidus as compared to standard cerebral arteriography fused to MRI.
Number of Subjects	14
Diagnosis and Main Inclusion Criteria	Patients with AVM requiring SRS, age ≥ 10 years. Size <= 3.5cm; <= 12cc
Study Product(s), Dose, Route, Regimen	Radiation, Stereotactic Radiosurgery with Gamma Knife, using standard of care, as directed by the treating Radiation Oncologist and Neurosurgeon.
Duration of administration	One day procedure
Reference therapy	Radiation, Stereotactic Radiosurgery of AVM using standard of care approach and MRI
Statistical Methodology	The target volume generated by IR angiogram will be compared to the target volume generated by CT angiogram using the Sorensen-Dice coefficient and surface to surface distance.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Arteriovenous malformation (AVM) is a congenital vascular malformation where there is direct arterial to venous connections without an intervening capillary network, creating a system of feeding arteries, tangled malformation or nidus, and draining veins engorged from the high pressure (Figure 1). Acting as a shunt, AVM results in a high pressure arteriovenous communication. The average annual risk of bleeding is 2–3 %[1]. Abnormal flow and a vascular "steal" phenomenon appear to be associated with larger AVMs and have been suggested to underlie some clinical symptoms associated with cerebral AVMs[2].

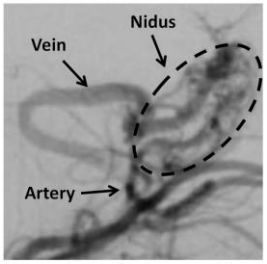


Figure 1: Feeding artery, nidus and draining vein of AVM

A combination of MRI and interventional cerebral arteriography is often used to assess the likely success and risks of surgical, endovascular, or stereotactic radiosurgery (SRS). Surgical resection remains the primary treatment modality for patients with AVM as it eliminates the source of hemorrhage. However, surgery may be intolerable in cases with AVM in deep locations and / or eloquent areas of the brain. Embolization may be used as an independent curative therapy, however, it is more commonly utilized prior to surgery as an adjunct (reviewed in [3]). SRS is another local treatment modality that has been established as an effective treatment for cerebral AVM[4]. Although commonly used, CT angiography for the treatment planning of SRS for AVM has not been validated against formal cerebral arteriography.

1.2 Stereotactic Radiosurgery (SRS)

SRS is an effective and minimally invasive approach compared to surgery. Its main drawback is the longer duration of time to achieve total obliteration of the AVM, ranging from six months to five years after the procedure[5]. Although the effect of SRS is not immediate, SRS is a preferable treatment option for patients with AVMs that are not surgically accessible or in patients with comorbidities that make them poor surgical candidates. In SRS, a potent dose of highly conformal radiation is delivered in a single fraction to the target nidus, leading to elimination in blood flow through the nidus in 40-80% of patients depending on AVM size[6]. SRS of AVM leads to the closure of the malformed vascular lumen, likely due to endothelial cell proliferation and fibrosis. In many centers that perform SRS, patients with AVM only undergo T1-weighted MRI image with gadolinium contrast to delineate the target volume. While MRI provide excellent soft tissue information, the AVM nidus is often difficult to be distinguished from the draining vein or a hematoma in the case of a previous hemorrhage, which leads to a treatment target considerably larger than the nidus itself. Other centers use volumetric CT angiograms to define the target.

At our institution, we routinely perform interventional cerebral arteriography on the day of the SRS procedure for improved target delineation. Following image acquisition, an neurointerventional specialist manually delineates the AVM nidus on the planar angiogram images; these images are stereotactically fused with the MR images. The nidus of the AVM is then contoured by the Neurosurgeon using the mutual information, to distinguish the AVM from a draining vein or the surrounding hematoma if there was prior hemorrhage. This extra information from the angiography allows the target volume to be significantly smaller compared to targets generated solely from MRI sequence, allowing us to spare the surrounding normal brain parenchyma. Even though the addition of angiography is time consuming and requires multi-modality team care, this approach has allowed our institution to treat the smallest possible target, yet achieve excellent obliteration rates of AVM with very low toxicity from the procedure. At our institution we also use CT angiogram at the treatment team's discretion to further enhance the accurate delineation of the final treatment

target volume. However, it had not been routinely done due to uncertain benefit in treatment planning and a concern for renal burden from additional intravenous (IV) contrast usage.

1.3 Rationale for the Protocol

While interventional cerebral arteriography is the gold standard for the diagnosis, treatment planning and follow up of AVM, it is an invasive procedure that comes with the risk of stroke (< 1 %), arterial dissection (< 0.5%), transient ischemia (< 3 %) and bleeding at the puncture site[7-11]. The risk of developing neurologic complications after the procedure appears to be elevated in patients with atherosclerotic cerebrovascular disease or cardiovascular disease, patients older than 55 years of age, and with fluoroscopic time beyond 10 minutes[11,12]. Interventional cerebral arteriography is also the gold standard in the diagnosis of acute ischemic stroke. Nevertheless, it is rarely performed nowadays as the primary diagnostic test in the acute setting. The main reason for the change in practice pattern is the advent of the noninvasive techniques such as CT and MR angiography and duplex and transcranial Doppler ultrasound that can rapidly visualize intracranial arterial disease. While SRS of AVM is not performed in the acute setting, performing a noninvasive angiogram instead of interventional arteriography will reduce the total treatment time by three to four hours. Such reduction in the procedure time will likely improve patient comfort and satisfaction as it will reduce the time these patient would need to wear the uncomfortable stereotactic headframe.

While noninvasive imaging with CT and MR angiography have still not replaced interventional cerebral arteriography, technical advances are allowing these modalities to serve as powerful adjuncts (reviewed in [13]). In fact, interventional cerebral arteriography only provides two-dimensional (2D) spatial information when combined with the gamma knife treatment planning system and requires an MRI of the brain for the 3D information (Figure 2) while CT or MR angiography provide 3D information that could be used in the treatment planning of SRS. However, the use of these reconstructed angiographic images for treatment planning of SRS has not been validated against interventional cerebral arteriography.

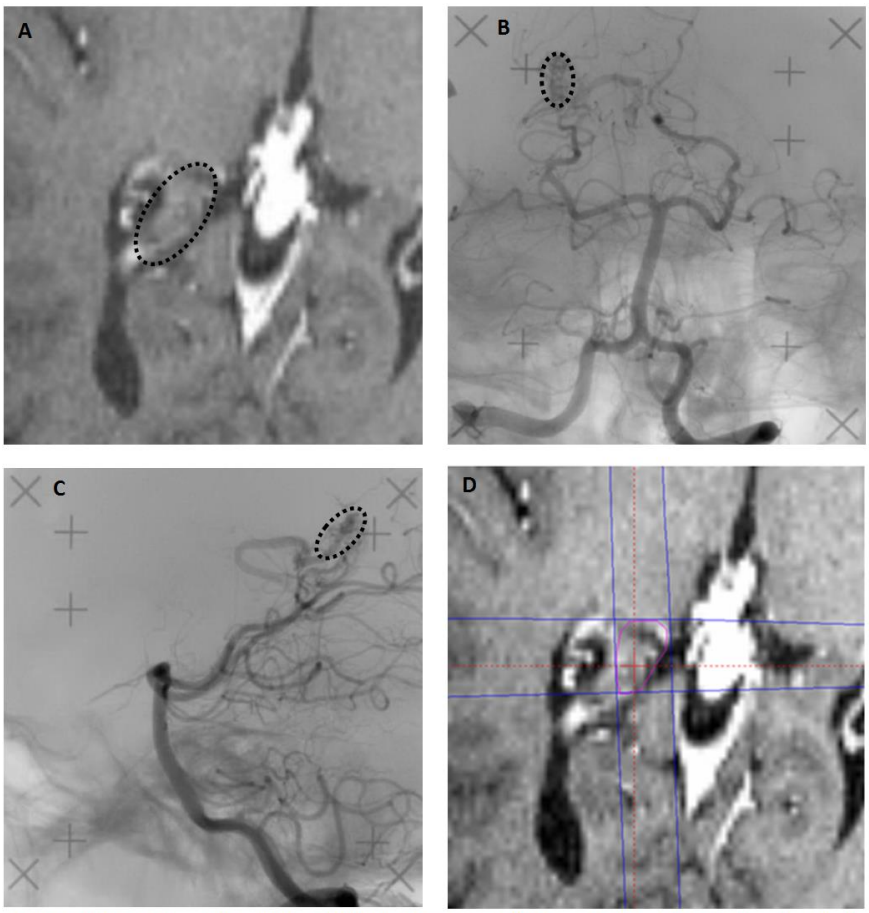


Figure 2: **(A)** Postcontrast T1 weighted MRI with a depiction of AVM target without interventional cerebral arteriography **(B)** Anterior-posterior (AP) and **(C)** right-left (RL) fluoroscopic images from cerebral arteriography used for nidus identification. X and + marks of the stereotactic frame depicted on these images enable fusion with MRI. **(D)** Fused MRI showing 2D nidus location from (B) and (C) projected as blue lines to delineate the nidus as target (pink outline).

Major risk factor for contrast agent-induced nephropathy is underlying renal dysfunction[14]. If a patient's renal function

is truly normal, then a high volume of contrast will not lead to nephropathy. In practice, however, the dose of contrast is a concern in patients undergoing catheter angiography and CT on the same day because certain doses are associated with adverse contrast reactions and nephropathy, although the data on this issue are limited[15]. Iopamidol (ISOVUE®) is the main intravascular contrast agent used at our institution. For multiple procedures on same day, the maximum recommended dose is 225 mL of ISOVUE-370 for adults and 125 mL for children between the ages of 10 to 18 (ISOVUE package insert, Bracco Diagnostic Inc, Cranbury, NJ). In these circumstances, due regard should be given to the clinical need for an optimal study with an adherence to the maximum recommended dose. In the vast majority of cases, contrast agent–induced nephropathy will be manifest by a transient increase in serum creatinine level, which usually peaks at 4–7 days and gradually returns to baseline[14]. A persistent elevation of serum creatinine level is unusual. Typically, both CTA and conventional angiography can be performed with less than 100cc of IV or IA contrast administration.

Finally, interventional cerebral arteriography adds an extra few hours to the overall clinic stay with an extra hour for the actual procedure, use of interventional radiology and recovery facility, and requires the patient to lay flat for several hours after the procedure due to the access of femoral artery. CT angiogram is expected to increase the procedure duration by another 15-30 minutes for transfer, set up and image acquisition. Although the patients enrolled on this study will endure approximately 30 minutes longer stay at the clinic, replacing the interventional cerebral arteriography with CT angiography in the treatment planning of SRS may ultimately reduce the total hospital stay by approximately three hours.

In summary, we propose to evaluate whether a target volume based on CT angiography can serve as a reliable substitute for a target based on interventional cerebral arteriography. Patients on this protocol will still get treated based on target generated by interventional cerebral arteriography but also receive CT angiography. If the target volume based on CT angiography are adequate compared to their invasive counterpart, future investigators may selectively omit performing interventional cerebral arteriography in the treatment planning for SRS of AVM. Use of CT angiography may lead to reduction in the risk from the procedure and cost, improve the efficiency of the treatment process ideally without compromising the success of the procedure, with greater patient comfort and satisfaction.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate whether target(s) based on CT angiogram can accurately and precisely identify the target nidus as well as an interventional cerebral arteriogram.

2.2 Secondary Objectives

2.2.1 To analyze and compare dosimetric parameters, including planning target volume (PTV) and V12, of an SRS treatment plan based on MRI alone, with interventional cerebral arteriography, and CT angiograms.

2.2.2 To evaluate the total time it takes to perform the additional CT angiograms and compare it to the duration of the interventional procedure.

2.3 Endpoints

The primary endpoint of this study is to compare the target generated from interventional cerebral arteriography (reference) to targets generated from CT angiogram and MRI alone, to assess whether noninvasive imaging approaches are non-inferior to the UTSW standard.

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 Documented AVM with draining vein(s).

3.1.2 Adequate renal function (serum Creatinine < 1.5 mg/dl within 30 days of SRS) to undergo contrast CT and interventional cerebral arteriography on the same day, as determined by treating physicians.

3.1.3 AVM must be physically separated from the optic pathway, brainstem or spinal cord.

3.1.4 The maximum diameter of AVM nidus must be less than 3.5 cm and/or less than 12 cc.

3.1.5 Age ≥ 10 years.

3.1.6 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 for the duration of study participation. 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).

3.1.7 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Patients without a documented AVM.

3.2.2 Patients with a contraindication to CT such as contrast allergy, kidney failure or implanted metal devices or foreign bodies or severe claustrophobia.

3.2.3 Use of Nephrotoxic drugs, such as gentamycin, high-dose nonsteroidal anti-inflammatory drugs, or certain chemotherapeutic drugs within 10 days of the procedure.

3.2.4 Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Patients must not be pregnant at the time of SRS treatment.

4.0 TREATMENT PLAN

This is not a therapeutic study, but rather a prospective imaging correlate study.

4.1 SRS Dose and Technique

CT angiogram and interventional cerebral arteriography will be obtained. CT angiogram may or may not be used for treatment planning as directed by the treating team. CT angiograms will be obtained in all patients to be potentially used in treatment and for protocol assessments.

4.2 Pre-therapy Assessment

Pre-therapy assessments will be performed as follows:

- Verify the patient has a documented AVM requiring radiation therapy.
- Verify age ≥ 10 years.
- Verify serum creatinine is age-appropriate with adequate renal function for various contrast reagents, within 30 days of SRS.
- Verify patient is not pregnant.
- Verify women of child-bearing potential and men agree to use adequate contraception
- Verify patient is able to understand and the willingness to sign a written informed consent.
- If any of the above criteria does not meet inclusion criteria, postpone SRS as appropriate.

4.3 Toxicities and Dosing Delays/Dose Modifications

The generally accepted safe upper limit total dose of iodinated contrast in one day is 225 mL of ISOVUE-370 for adults and 125 mL for children between the ages of 10 to 18. The amount of the administered contrast may be exceeded at the knowledgeable direction of the treating radiologists. All patients enrolled on the study will be assessed for the development of toxicity according to the Time and Events table (5.3) should the subject receive more than the recommended dose of contrast. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Contrast related allergic reactions will also be monitored per CTCAE criteria. Only AEs reported to Radiation Oncology discipline per study calendar will be captured and assessed.

4.4 Post therapy Assessment

This is not a therapeutic study, but rather a prospective imaging correlate study.

4.5 Post therapy Intervention

- Serum creatinine will be checked 1 week (-3 days/+7 days) after the procedure and again at 1 month (+/- 10 days) after procedure.

4.6 Duration of Therapy

CT Angiogram will be obtain without exceeding the limits of IV contrast before SRS administration (SRS is not a part of this protocol), which typically be completed in one day. CT Angiogram will proceed unless:

- 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 stereotactic team.

4.7 Duration of Follow Up

Nearly all the information needed for the protocol will be collected on the day of the procedure. Only AEs reported to Radiation Oncology discipline per study calendar will be captured and assessed. No follow up of AVM outcome is assessed as part of this protocol.

4.8 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 Investigator, and document the reason for study removal 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 90 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 Review subject eligibility criteria

5.1.4 Review previous and concomitant medications

5.1.5 Physical exam

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

5.1.6 Adverse event assessment

See section 7 for Adverse Event monitoring and reporting.

5.1.7 Serum Creatinine

5.1.8 Pregnancy test (for females of child bearing potential)

See section 3.1.6.1 for definition.

5.2 Follow-up Procedures

This is not a treatment study, and the subject will not be followed for AVM outcome for the purpose of this study. Serum creatinine value will be checked 1 week (-3 days/+7 days) after the procedure and 1 month (+/- 10 days) after the procedure.

5.3 Time and Events Table

	Pre-study[1]	Day 0	1 Week (-3 days, +7 days)	1 Month (+/- 10 days)
Informed Consent	X			
History and PE	X			
Serum Creatinine[2]	X		X	X
Interventional Cerebral Arteriography		X		
CT Angiogram		X		
Adverse Event Assessment		X[3]	X[3]	X[3]

1 – All screening procedures must be performed within 90 days prior to registration unless otherwise stated
2 – Within 30 days of SRS procedure
3 – Only if subject receives more than the recommended dose of contrast

5.4 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:

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

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

5.4.3 Subject is unable to comply with protocol requirements;

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

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

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

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

5.4.8 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;

5.4.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented

6.0 Measurement and evaluation of AVM targets

6.1 AVM Target

Quantitative analysis of the accuracy of the experimentally generated targets will be performed in this study based on two established methods of segmentation geometric accuracy evaluation (see section 6.1.2).

6.1.1 Definitions

Target: Target is the AVM nidus (figure 1) excluding the feeding artery and draining vein or hemangioma, if present.

Reference Target lesion: AVM nidus identified using interventional cerebral arteriography superimposed to MRI of brain +/- CT angiography (CTA), per treatment team discretion that is used in the actual SRS treatment.

CTA Target lesion: AVM nidus identified using CT angiogram of the brain alone, at a later date (greater than one month later) in a blinded manner, by the Neurosurgeon who contoured the reference target lesion.

MRI Target lesion: AVM nidus identified using MRI of the brain alone, at a later date (greater than one month later) in a blinded manner, by the Neurosurgeon who contoured the reference target lesion.

6.1.2 Evaluation and comparison of targets

Two methods of segmentation geometric accuracy evaluation, Dice coefficients and Hausdorff distance analysis, will be utilized to compare the reference target generated from interventional cerebral arteriography to targets generated from CT angiograms.

6.1.2.1 Dice Coefficients (DCs = 2(A∩B)/(A+B)), where A and B are the ground-truth and evaluated as segmented volumes, respectively. Dice coefficient is a simple spatial overlap index and a reproducibility validation metric[16] and a reproducibility validation metric, which has been adopted to validate the segmentation of white matter lesions in MRI[17] and brain tumors[18]. The value of a Dice Coefficients ranges from 0, indicating no spatial overlap between two sets of images, to 1, indicating complete overlap.

6.1.2.2 Hausdorff distance (HD) between two finite point sets A and B is defined by HD(A, B) = max (h(A, B), h(B, A)), where h(A, B) =$\max_{a\epsilon A}\min_{b\epsilon B}$Ila-bIl Spatial distance based metric, such as HD, is widely used in the evaluation of image segmentation when the segmentation overall accuracy, such as the boundary delineation (contour), of the segmentation is of importance[19].

6.2 Safety/Tolerability

IV hydration will be initiated prior to all radiosurgery procedures and continued as needed until discharge. Patients will be instructed to increase hydration after the procedure and report to the treating physician in the event of developing decrease in urine output, new or worsening of swelling in extremities or around the eyes, fatigue, shortness of breath, chest pain or pressure, confusion or seizure to prevent kidney injury.

- Serum creatinine will be checked 1 week (-3 days/+7 days) after the procedure and again at 1 month (+/- 10 days) after the procedure.

7.0 ADVERSE EVENTS

7.1 Kidney Injury

7.1.1 Contraindications: Contrast allergy, underlying significant renal dysfunction or renal failure.

7.1.2 Special Warnings and Precautions for Use: The generally accepted safe upper limit total dose of iodinated contrast in one day is 225 mL of ISOVUE-370 for adults and 125 mL for children between the ages of 10 to 18. The amount of the administered contrast may be exceeded at the knowledgeable direction of the treating radiologists.

7.1.3 Interaction with other medications: Nephrotoxic drugs, such as gentamycin, high-dose nonsteroidal anti-inflammatory drugs, or certain chemotherapeutic drugs.

7.1.4 Adverse Reactions: Sites-specific. Please see section 7.2.

7.2 Contrast Reactions

Acute contrast reactions occur within minutes of administration of iodinated contrast. An estimated 3% of patient will experience mild contrast reaction that requires no treatment. However, moderate reactions such as bronchospasm or hypotension can occur in about 1 in 250 patients (0.4%) and about 1 in 1600 to 2500 (0.04-0.06%) of patients could experience a severe reaction [20].Treatment consist of administering medications directed at the specific cause of symptoms, such as bronchospasm with beta-2 agonist inhaler, while an airway or laryngeal edema should be treated with epinephrine. Antihistamine and/or corticosteroids could be administered if necessary. Delayed adverse reactions develop more than one hour after the procedure but within 7 days of IV contrast administration. It is mild in majority of cases and resolve without intervention. Non-specific symptoms range from Flu-like illness, arthralgia, aches and pains, parotitis, fever,

abdominal pain and headache. Treatment consists of antihistamine and/or corticosteroids. Severe cases may require a referral to a dermatologist.

7.3 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 using similar agents. 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 that is reported to Radiation Oncology discipline per study calendar, 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 treatment for the changes observed; or
- Death.

7.3.1 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 1 month (+/- 10 days) post treatment planning procedure (CT angiogram) will be considered acute adverse events. Only kidney-specific adverse events will be followed should the subject receive more than the recommended dose of contrast, according to good medical practices. Acute adverse events, that are collected as specified within the protocol, will be assessed and reported as per below.

Late Adverse Events

Adverse effects occurring in the time period after the end of acute monitoring will be defined as late adverse events. Late adverse events will not be captured, assessed, graded or reported.

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 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 prolongs 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.

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, as specified in section 7.3, will be followed up according to good medical practices.

Kidney-specific adverse events will be followed up should the subject receive more than the recommended dose of contrast, according to good medical practices.

7.4 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 within the acute adverse events reporting period as defined in section 7.3 and is attributed (possibly, probably, or definitely) to the treatment planning procedure (CT angiogram).

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

7.4.1 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.

Telephone reports to: Sarah Neufeld, Management Analyst 214-648-1836
Written reports to: Department of Radiation Oncology Clinical Research Office The University of Texas Southwestern Medical Center Attention: Sarah Neufeld, Project Manager 2201 Inwood Road Dallas, Texas 75390-9303 FAX #: 214-648-5923 UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306

UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

7.4.2 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/

7.5 Stopping Rules

The study is designed to end if the rate of kidney injury from multiple contrast usage is higher than expected despite meeting the maximum recommended dose of contrast or an inability to consistently meet the recommended dose of contrast.

8.0 DRUG INFORMATION

ISOVUE 300 and 370 ® are products of Bracco Diagnostics, Inc, Cranbury, NJ. Per the ISOVUE package insert, the maximum recommended dose of ISOVUE-370 for multiple procedures is 225 mL for adults and 125 mL for children between the ages of 10 to 18. ISOVUE is the brand currently used by UTSW hospitals. There are other vendors of iodinated contrast and UTSW's utilization may change.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

The primary endpoint of this study is to compare the target generated from interventional cerebral arteriography (reference) to targets generated from CT angiogram and MRI alone, to assess whether noninvasive imaging approaches are non-inferior to the UTSW standard.

9.2 Sample Size estimate

Each patient will have measurements of Dice similarity coefficients for both invasive and noninvasive approaches. A previous study[21] showed that the mean for Dice similarity coefficient of the AVM nidus between CTA and MRI was 0.765 and the standard deviation was 0.0894. A sample size of 14 patients achieves 92% power to detect non-inferiority using a one-sided t-test with a significance level of 0.05 when the margin of non-inferiority is -0.077 (10% margin) and the true difference between the mean of invasive approach and non-invasive approach is 0.0. Sample size was estimated using a non-inferiority test for one mean in PASS 14 software.

9.3 Data Analysis Plans

Interim reports will be prepared every six months until 35 days after the last patient is enrolled. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of and compliance rate of target generation from CT angiogram and MRI alone per protocol, and the frequencies and severity of renal toxicity of the subjects.

10.0 STUDY MANAGEMENT

10.1 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.

10.2 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.

10.3 Required Documentation (for multi-site studies)

Not applicable for this protocol.

10.4 Registration Procedures

All subjects must be registered in Velos before enrollment to the study. Prior to enrollment, eligibility criteria must be confirmed with the study coordinator.

The first subject enrolled at UTSW will receive a number beginning with 101 and each patient enrolled thereafter will have a sequential ID number (i.e. 102, 103, 104).

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".

10.5 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.

Toxicity reviews will be performed, via the interim reports, every 6 months until 35 days after the last patient is enrolled. These reviews will be documented by the study team and/or the UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC).

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.

10.6 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.

10.6.1 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.

10.6.2 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.

10.6.3 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 to the IRB within 5 working days of discovery.

10.6.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in one 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.

10.6.5 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

10.7 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.

10.8 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.

10.9 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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