RAD 1501: A Phase II Trial of Virtual Cone Trigeminal Neuralgia Radiosurgery

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Summary of Amendment # 1 (Protocol Version: August 2, 2016)

Removal of requirement to treat first ten patients with invasive stereotactic frame. All patients will be treated frameless with optical monitoring.

Summary of Amendment #2 (Protocol Version: April 25, 2018)

Update of toxicity of initial 17 patients.

Addition of 20 patients at UAB prior to future amendment supporting multi-institutional enrollment.

Document History Table

	Version/Update Date
Original Version	June 5, 2015
Protocol Update	September 14, 2015
Amendment # 1	August 2, 2016
Amendment # 2	April 25, 2018

LIST OF ABBREVIATIONS

BNI	Barrow Neurologic Institute Pain Intensity Score
CTCAE	Common Terminology Criteria for Adverse Events
RS	radiosurgery
SAE	serious adverse events
TGN	trigeminal neuralgia
UAB	University of Alabama at Birmingham

1.0 OBJECTIVES

Primary objective:

- **Stage I (Pilot at UAB Only, Single Institution)**
  - To determine the feasibility of frameless Virtual Cone trigeminal neuralgia radiosurgery at a single institution prior to multi-institutional enrollment.
- **Stage II (Multi-Institutional)**
  - To measure pain relief after Virtual Cone radiosurgery utilizing the Barrow Neurologic Institute Pain Intensity Score (BNI).

Secondary objectives:

- To define the acute and late neurologic toxicity up to one year after Virtual Cone radiosurgery for trigeminal neuralgia (CTCAE 4).
- To assess quality of life changes associated with Virtual Cone radiosurgery as measured by SF-36.
- To assess patient satisfaction with frameless Virtual Cone radiosurgery as measured by questionnaire.

Exploratory objectives:

- To obtain a preliminary estimates of patient satisfaction with frameless virtual cone procedure.

2.0 BACKGROUND AND RATIONALE

2.1 Definition of Trigeminal Neuralgia (TGN)

Trigeminal neuralgia is a sudden, severe sharp or lancinating pain involving one side of the face. Also know as *tic doulourex*, trigeminal neuralgia is thought to impact 45,000 people in the United States. The pain can be spontaneous or a stimulation trigger involving one or more branches of the trigeminal nerve. The cause is often vascular compression of the trigeminal nerve in close proximity to the brainstem. The most widely utilized classification of facial pain was proposed by Burchiel. (Burchiel, 2003) Classic idiopathic trigeminal neuralgia is also known as type I in the Burchiel classification and reflects pain that is episodic at least 50% of the time. Pain that is constant more than 50% of the time is type II.

2.2 Overview of Treatment Options

Primary therapy for trigeminal neuralgia is medical with front line treatment generally carbamazepine (Tegretol). Other medications may include baclofen and gabapentin.

Secondary treatments include a variety of local procedures including microsurgical decompression, glycerol injection, and radiosurgery. For appropriately selected cases microsurgical decompression provides a more effective and longer lasting pain relief than other

secondary procedures. Therefore, radiosurgery is most often performed after one of more other treatments has failed or when medical therapy is not tolerated. Because radiosurgery is the least invasive treatment option it is often the treatment of choice for older patients that have not responded to medical management.

2.3 Radiosurgical Target and Dose

The initial dose and target volumes for trigeminal neuralgia were selected based upon the dose required to ablate tissue at others sites in the brain. Most of the larger retrospective studies were performed utilizing the Leksell Gamma Knife treatment unit and demonstrate that about 80-90% of properly selected patient respond. As single institution and retrospective studies became available, there were concurrent reports regarding the accuracy of the "4 mm helmet" dosimetry employed on the Gamma Knife (Ma, Li, & Yu, 2000). These eventually led to a change in the calibration for the 4 mm helmet and revisions in the radiosurgical dose prescription to match the actual dosimetry. For example, at UAB the prescription was changed from 80 Gy to 87 Gy to maintain the same clinical dose when the new output factors were implemented. It is important to interpret the historical literature in the context of this dosimetry inaccuracy.

The most commonly employed doses for trigeminal neuralgia radiosurgery have ranged from 70 to 90 Gy prescribed to a maximal point. Pollock et al found that 90 Gy (old output factor) was associated with a higher risk of permanent complications including over half of patients developing numbness in the high dose group(Pollock, Phuong, Foote, Stafford, & Gorman, 2001). The most commonly reported complications of trigeminal neuralgia radiosurgery are facial numbness and corneal dryness with less common complications being facial weakness, brainstem injury, or anesthesia dolorosa.

Historically, some linear accelerator (linac) based approaches have treated a longer length of nerve than is most common with the Gamma Knife. Flickinger et al randomized eighty-seven patients to one versus two "shots" radiosurgery(Flickinger et al., 2001). The longer length of nerve treated with two shots did not improve pain relief and treatment of the longer nerve length was associated with an increase in new numbness or paraesthesia. For this clinical trial the goal of the associated preclinical work was to mimic the dose distribution of the 4 mm helmet with a **single** shot.

The efficacy of Gamma Knife radiosurgery for trigeminal neuralgia has been studied prospectively and has been modeled based upon prognostic factors in larger retrospective studies. These studies provide benchmarks for measuring the safety and efficacy of Virtual Cone Radiosurgery. Instruments to score pain include the BNI (appendix) or a variation termed the Regis criteria. Regis et al performed a prospective clinical trial of Gamma Knife radiosurgery (70-90 Gy). (Régis et al., 2006) With variable follow-up, 83% of patients were "pain-free" (with or without medication) at the last follow-up. The probability of being "pain-free" at one year was 70% (estimated from a Kaplan-Meier curve). Investigators from Wake

Forest University have recently published a nomogram to predict pain improvement after radiosurgery. Overall they found that 84.5% of patients were free from BNI 4/5 pain at one year. (Lucas et al., 2014) **In the current trial the investigators are expecting that 75% of patients will be free from BNI 4/5 pain at one year.** Additional details of the statistical analysis plan can be found in Section 11.

2.4 Virtual Cone Preclinical Studies

Recent improvements in MLC and linac design have reduced leaf leakage, improved accuracy, and have greatly improved treatment efficiency. Associated with these advances, improved image guidance and intrafraction monitoring should facilitate possible frameless radiosurgery procedures even on very small functional targets very close to critical structures (e.g. trigeminal neuralgia radiosurgery). Recently, investigators at UAB have described an MLC-based delivery configuration for the TrueBeam linac with HD-MLC that mimics the dosimetry of the Leksell Gamma knife 4 mm helmet (see **Figure 1 and Figure 2**). This technique has been termed the "Virtual Cone" and does not require patient-specific beam fluence and thereby avoids patient-specific quality assurance dose measurements facilitating workflow for possible same day treatment. Dosimetry measurements confirm that the Eclipse treatment planning system accurately calculates the Virtual Cone dose distribution. Initial measurements of this technique at 2400 mu/min suggest treatment could be completed in 20 minutes or less after alignment. A recent trajectory-based version of the

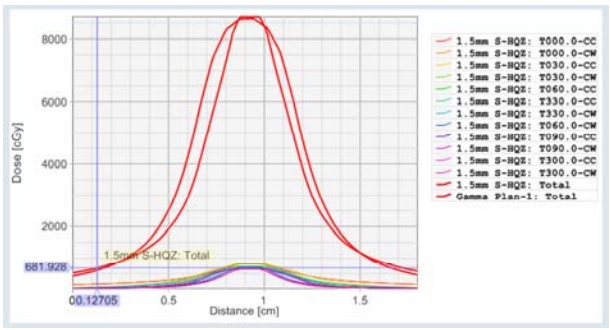
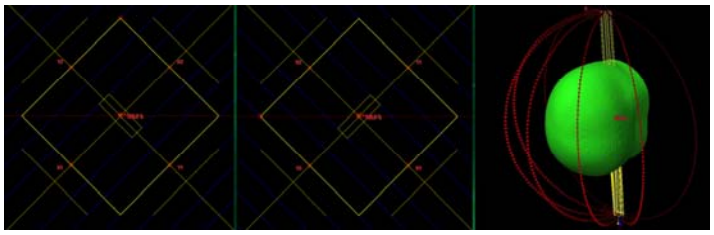


Figure 1 Dose profile of Virtual Cone and 4mm Gamma Knife helmet. The Virtual Cone is the slightly more narrow curve.



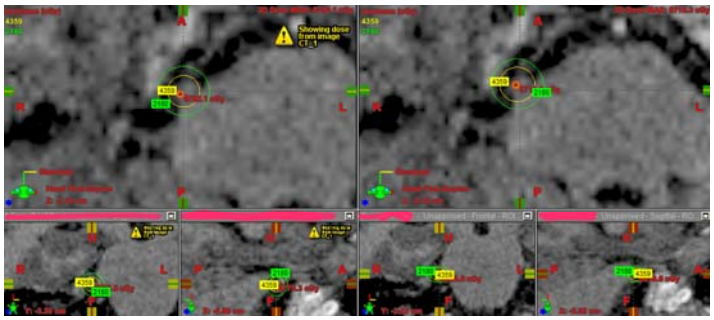


Figure 2a (upper) MLC aperture and arc geometry of the Virtual Cone. **Figure 2b (lower)** Clinical comparison of Gamma Knife and Virtual Cone radiosurgery plan shown on the same MRI dataset. Prescription dose is 87 Gy to D_{max}. The yellow (50%) and green (25%) isodose suggest similar dosimetry.

virtual cone was developed that does not require room entry and has delivered 87 Gy in 13 minutes.

In order for possible frameless Virtual Cone radiosurgery to be a standard of care in the treatment of trigeminal neuralgia, additional clinical data is required. Historically, some physicians have not considered linacs accurate enough for functional radiosurgery, but the mechanical accuracy of the TrueBeam and Edge platforms challenges this notion. Larger clinical series and prospective clinical trials have not been performed utilizing linacs, especially for frameless delivery. We propose a multi-institutional phase II trial of Virtual Cone radiosurgery to assess the safety and efficacy of this treatment. Prior to starting the multi-institutional portion of the trial a pilot study of forty patients will be treated at UAB to confirm the feasibility of the protocol procedures and safety of the treatment (feasibility is defined in 11.1). Secondary endpoints will include quality of life and patient satisfaction. Enrollment would be in two stages with the first forty patients enrolled at UAB and then adding additional centers to complete one hundred patients. A protocol amendment will be required prior to starting stage II. **We hypothesize that the recent improvements in linac delivery, image guidance, and patient position monitoring will allow a safe frameless procedure that has a high patient satisfaction and low toxicity.**

2.5 Rationale Frameless Treatment

Radiosurgery has traditionally required a stereotactic frame for localization and immobilization. Prior to this trial all trigeminal neuralgia radiosurgery patients at UAB have been treated with a stereotactic frame on the Gamma Knife, but frameless treatments are more common on other radiosurgery devices (e.g. Cyberknife). Frameless radiosurgery has been employed in hundreds of patients at UAB for other indications.

In this study the localization procedure will be based upon kilovoltage orthogonal x-rays, cone beam CT scanning, and optical surface imaging. These are all FDA approved imaging tools commonly utilized in the treatment of cancer patients with fractionated radiation therapy. The most recently available imaging tool in this trial is the optical surface monitoring. Utilizing optical surface imaging, the treating physician can monitor the patient's face and forehead for movement in real-time with sub-millimeter accuracy. When this trial was initially activated the optical imaging was not clinically available at UAB. At that time the study plan included the initial ten patients to be treated with a stereotactic frame. The Edge linac with optical imaging was installed and commissioned June 2016. It is anticipated that all linac radiosurgery at UAB will be frameless going forward. The use of a frame has also been a barrier to patients electing to enroll. The August 2016 amendment allows all patients to be treated frameless.

2.6 Initial Clinical Experience of Pilot (April 25, 2018 Amendment # 2) and Enrollment Plans

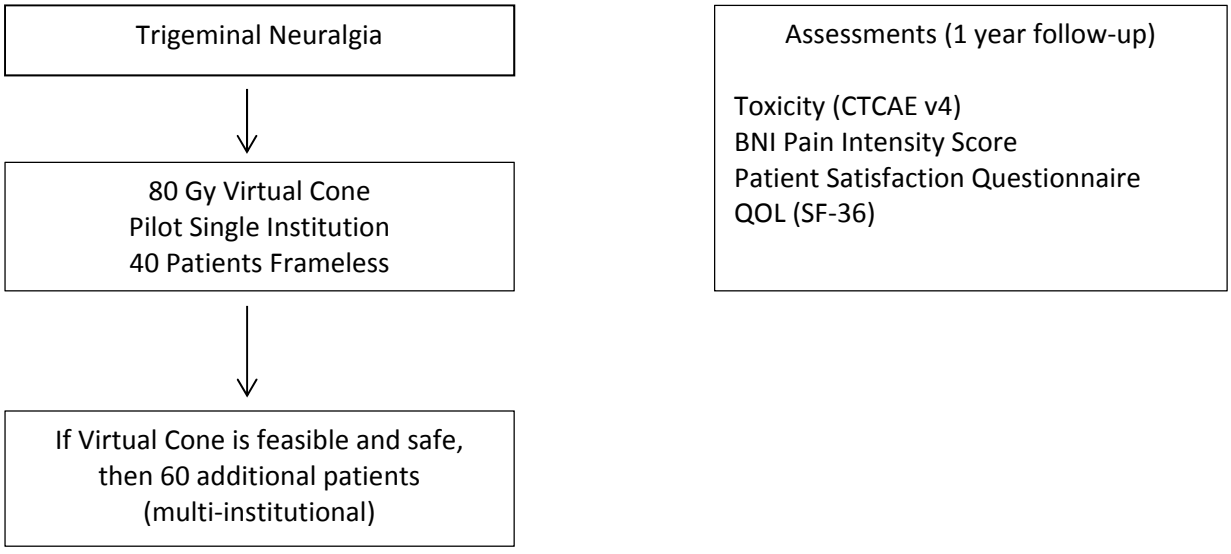
Seventeen patients have been treated with eighteen enrolled (one patient pending treatment). Seven patients have completed the three month toxicity visit with no serious adverse events. Treatment response is favorable with 7/8 patients satisfied with pain response. The clinical workflow is now well established.

UAB is currently in talks with potential other sites for the multi-institutional portion of the trial but those contracts have not been finalized. For now, we plan alter enrollment plans to proceed with forty total patients at UAB (expansion from twenty) with plans for future amendment describing the multi-institutional enrollment process to achieve a total enrollment of one hundred patients.

3.0 SCHEMA

This trial will initially enroll forty patients at a single institution to confirm that all study procedures and assessments are feasible and safe. An additional sixty frameless patients will be enrolled in a multiple institutional study (total one hundred patients).

Schema:



4.0 PATIENT SELECTION CRITERIA

4.1 Inclusion Criteria

4.1.1 Patients with trigeminal neuralgia pain that is not well controlled despite medical management (BNI 4 or BNI 5).

4.1.2 Patients must have an ECOG status of 0, 1, or 2.

4.1.3 Patients must be at least 18 years of age.

4.1.4 Life expectancy must be greater than 12 months.

4.1.5 MRI of brain within prior 12 months to confirm lack of other causes of facial pain.

4.1.6 All patients must be given written informed consent.

4.2 Exclusion Criteria

4.2.1 Patients who have had prior brain radiosurgery or therapeutic radiation therapy to the pons.

4.2.2 Patients with atypical trigeminal neuralgia or headache pain syndromes.

4.2.3 Patients with pain associated with multiple sclerosis or base of skull tumor.

4.2.4 Patients with medical contra-indications to MR imaging (e.g. pacemaker).

5.0 DRUG INFORMATION

5.1 No experimental drugs will be used as a part of this study.

5.2 Standard of care medications are prescribed at the discretion of the treating physician including pain medications and steroids on the day of treatment.

6.0 TREATMENT PLAN

6.1 Radiosurgery Parameters

6.1.1 All radiosurgery treatment will utilize a Varian Edge or TrueBeam Linac with high definition MLC (HD-MLC) and a 6DOF couch.

6.1.2 Beam delivery can be 6MV or 10MV utilizing a high intensity mode or flattening filter free beam operating at up to 1400-2400 MU/min.

6.1.3 Radiosurgery will be administered with the virtual cone technique.

6.1.4 Prescription dose is 80 Gy to Dmax.

6.1.5 Target is dorsal nerve root entry zone with edge of brainstem receiving 30-50% of prescription 80 Gy. This target will be defined on CT/MR fusion. CT slice thickness should be 1.5 mm or less and MR slice thickness must be 2.5 mm or less.

6.2 Virtual Cone Credentialing

Prior to starting the multi-institutional portion of the trial (Stage 2), all centers will undergo a credentialing process to include treatment of a phantom and transfer of the treatment data to the central office. The full description of the credentialing process will be included in an amendment that will be submitted prior to starting the multi-institutional stage of the protocol.

6.3 Evaluation Metrics

6.3.1 CTCAE 4.0

All adverse events will be scored utilizing the Clinical Terminology Criteria for Adverse Events (version 4.03). http://evs.nci.nih.gov/ftp1/CTCAE/About.html

In addition to scoring of adverse events with the CTCAE scale, any event involving dysfunction of the trigeminal nerve will be descriptively characterized by the physician investigator including any numbness, corneal anesthesia, hypoesthesia, dysesthesia, deafferentation pain, or anesthesia dolorosa.

6.3.2 BNI Pain Intensity Score

This evaluation was designed to assess trigeminal neuralgia associated pain and has been utilized in several prior studies of radiosurgery. The score is detailed in the Appendix A.

6.3.3 Quality of Life (QOL)

Quality of life will be measure by SF-36 developed by the Rand Corporation. This standard measure of quality of life has been commonly employed in clinical trials. Additional background and scoring instructions can be found at http://www.rand.org/health/surveys_tools/mos/mos_core_36item.html

The specific pdf of the questionnaire will be available to investigators on the RedCap website.

6.3.4 Patient Satisfaction

Prior studies of patient satisfaction have utilized simple or complex questionnaires. The questionnaires with the best described methodology overlap with the BNI and SF-36 instruments planned for this study. For future clinical decision-making two questions were selected and have been used in recent studies:

1) Would you have the radiosurgery procedure again?
2) Would you recommend it to friends or family?

The specific pdf of the questionnaire will be available to investigators on the RedCap website.

7.0 THERAPY MODIFICATIONS

7.1 No therapy modifications are planned.

7.2 If for any reason other than toxicity, a patient does not complete the three-month toxicity assessment, this patient will be replaced.

8.0 STUDY PARAMETERS

8.1 Toxicity evaluations occur at one month, 3 months, 6 months, and 12 months. The one-month appointment can occur within 14 days of the specified date. The 3, 6, and 12-month appointments can occur within 30 days of the specified date. Study follow-up will cease at 1 year following the completion of radiosurgery.

8.2 Day 0 is defined as the day of radiosurgery.

	Baseline	**Radiosurgery***	**1 mo.**	**3 mo.**	**6 mo.**	**12 mo.**
History and Physical Exam including ECOG PS	X[1]		X	X	X	X
CTCAE (toxicity evaluations)		X	X	X	X	X
BNI Pain Intensity Score	X	X	X	X	X	X
QOL (SF-36)	X		X	X	X	X
Medication Record	X	X	X	X	X	X
Patient Satisfaction Questionnaire				X		
[1] Baseline assessment must be within 30 days of radiosurgery						

*As part of the radiosurgery procedure, all patients will have a CT simulation and MRI.

9.0 EVALUATION CRITERIA and ASSESSMENTS

9.1 Pretreatment, day of radiosurgery, and follow-up assessments are shown in the table in Section 8.2. If a patient is unable to complete treatment or assessments, the investigator should indicate the reason (e.g. treatment could not be completed due technical issue, patient anxious and unable to be compliant with positioning, etc.).

9.2 Data will be recorded to a central RedCap database administered by the UAB Department of Medicine. Access procedures and HIPPA compliance information on this infrastructure can be found at http://www.uab.edu/medicine/dom/redcap/137-it/152-redcap

9.3 Adverse event reporting will be according to the UAB Data Safety and Monitoring Plan. This includes monthly reporting to the Clinical Trials Monitoring Committee for all adverse events. Serious adverse events are also reported to the UAB IRB and the study PI within 24

hours. *The data safety and monitoring plan for stage II will be specified in an amendment prior to multi-institutional enrollment.*

9.4 A *Serious Adverse Event* (SAE) is defined as any adverse event that suggests a significant hazard, contraindication, side effect, or precaution. A serious adverse event includes any experience that is:

- Death or life threatening
- Requires or prolongs hospitalization
- Congenital anomaly
- Persistent or significant disability/incapacity
- Important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes
- Any additional adverse experiences that FDA or the study protocol has defined as serious.

9.5 Causality

The Investigator will assess the causality relationship of the radiosurgery to a serious adverse event as follows:

- Unrelated: There is no evidence of causal relationship
- Unlikely: There is *little* evidence to suggest there is a causal relationship (*e.g.,* the event did not occur within a reasonable time after administration of the radiosurgery). There is *another reasonable explanation* for the event (e.g., the pat*ient's clinical condition, oth*er concomitant treatments).
- Possible: There is *some* evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the radiosurgery). However, the influence of *other factors may have contributed* to the event (e.g., the patient's clinical condition, other concomitant events).
- Probably: There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.
- Definite: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

10.0 PATIENT REGISTRATION

Patients can be registered by calling John Fiveash 205-975-0224 or Laronica Conway at 205-975-4362.

11.0 STATISTICAL CONSIDERATIONS and ANALYSIS PLAN

11.1 Sample Size

The study includes a feasibility-testing phase (Stage I) to determine the feasibility of frameless virtual cone radiosurgery for trigeminal neuralgia and an expansion phase (Stage II). The sample size for Stage I will include 40 patients. An additional 60 patients will be enrolled in to Stage II.

The procedure will be judged feasible if two criteria are met in stage I:

1) At least 38 of 40 enrolled patients complete treatment and assessments at the three-month follow-up.
2) No more than 1 of 40 develops irreversible grade 3 or greater acute CTCAE 4.0 toxicity within the three month follow-up judged possibly or likely or definitely related to radiosurgery treatment.

After the feasibility of the assessments and treatment has been demonstrated in stage I, an additional 60 patients will be enrolled at 3-5 centers. Assuming this study would achieve a one-year (BNI 4 or 5 pain free) rate of 75%, 95 patients will be required to produce a two-sided 95% confidence interval with a width equal to 18.3 (65.1-83.3) using Exact (Clopper-Pearson) method. Assuming a 5% drop out, a total of 100 patients will be accrued to the study.

The accrual rate in the pilot is expected to be 1-2/month. Accrual rate of stage II will be determined based upon number of institutions participating and will be defined in a protocol amendment.

11.2 Data Analysis

In general, descriptive statistics will be used to summarize the feasibility and efficacy variables collected and the baseline demographic data. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. For time-to-event variables, Kaplan-Meier plots, median time-to-event, and other percentiles may be presented. The parameters of interest and their 95% confidence intervals will be estimated using exact methods. BNI Score will be calculated in treated patients that are considered evaluable. The primary outcome is the overall pain reduction proportion (as evaluated by BNI 4 or 5 pain free) at 12 months after treatment, and will be computed based on the collected data. Corresponding 95% confidence interval will be estimated. We will conduct secondary analyses on the complete time profile for the pain and QOL measurements through one-year of follow-up using methods appropriate for

the analysis of repeated measures such as linear mixed models or repeated measures ANOVA. Additional exploratory analyses of the data will be conducted as deemed appropriate.

11.3 Analysis of Safety

All patients who receive treatment in this study will be included in the ongoing safety analysis. Patient will be monitored during the treatment period and queried at each follow-up visit for Adverse Events (AEs). All AEs will be graded by using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). All AEs will be tabulated and examined for a treatment effect. The safety analysis will be performed on the total sample size.

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APPENDIX A: Barrow Neurologic Pain Intensity Score (BNI)

Score	
I	No trigeminal pain, no medication
II	Occasional pain, not requiring medication
III	Some pain, adequately controlled with medication
IV	Some pain, not adequately controlled with medication
V	Severe pain/no pain relief

APPENDIX B: Physics Credentialing

- **Details will be added in future amendment prior to starting the multi-institutional portion of the trial.**