Study Title: A Phase II Pilot Trial of Preoperative SRS/SRT versus Postoperative SRS/SRT for Brain Metastases (NCT04422639)

Principal Investigator: Analiz Rodriguez MD, PhD
Director of Neurosurgical Oncology
Assistant Professor
Department of Neurosurgery
University of Arkansas for Medical Sciences

Co-Investigator (s): Fen Xia, MD, PhD
Professor and Chair
Department of Radiation Oncology
University Arkansas College of Medicine

Gary D. Lewis, MD
Assistant Professor
Department of Radiation Oncology
University Arkansas College of Medicine

Manoj Kumar, MD
Associate Professor
Department of Radiology, Neuroradiology

Mausam Patel, MD
Resident Physician
Department of Radiation Oncology
University Arkansas College of Medicine

Sub-Investigator (s): Leslie Harrell, DO
Professor
Department of Radiation Oncology
University Arkansas College of Medicine

J.D. Day, MD
Professor and Chair
Department of Neurosurgery
University of Arkansas for Medical Sciences

T.W. Morris, III, MD
Assistant Professor
Department of Neurosurgery
University of Arkansas for Medical Sciences

Viktoras Palys, MD
Assistant Professor
Department of Neurosurgery
University of Arkansas for Medical Sciences

Study Statistician:

Eric R. Siegel, MS
Biostatistics Project Manager
Department of Biostatistics
University of Arkansas for Medical Sciences

Study location:

University of Arkansas for Medical Sciences

Background and Rationale

The incidence of brain metastases has been rising in recent years.[1] As a result, the optimal management of patients with brain metastases is a topic of important concern. For a patient with a single or solitary brain metastasis, surgical resection has been associated with improved survival.[2] Surgical resection is also an important option for patients with large brain metastases causing mass effect or symptoms. However, surgical resection alone, even with a gross total resection, is associated with high rates of local recurrence (on the order of 50%), likely due to tumor spill.[3] As a result, post-operative adjuvant radiotherapy has been used to reduce the rate of local recurrence.

Work by Patchell et al. demonstrated that whole brain radiotherapy (WBRT) after surgical resection of a single brain metastasis reduced the rate of recurrence at the site of the original metastasis and at other sites of the brain.[3] It also decreased the likelihood of death from neurologic causes. However, WBRT is not without side effects; there is particular concern with the long-term neurocognitive effects of treatment.

As a result, postoperative stereotactic radiosurgery (SRS) and less than 5 fractions of stereotactic radiation therapy (SRT) has become increasingly popular. SRS/SRT delivers high doses of radiotherapy via multiple beam angles and highly conformal planning techniques to the target, sparing normal brain tissue. A randomized trial by Brown et al. found that postoperative SRS had similar overall survival (OS) when compared to postoperative WBRT (median OS of 12.2 months vs. 11.6 months, respectively [$p = 0.70$]) but had lower rates of cognitive deterioration (52% vs 85% [$p<0.001$]).[4] When compared to observation after surgery, a separate trial demonstrated improved local control with postoperative SRS.[5]

There is growing interest in whether SRS/SRT delivery for brain metastases can be transitioned to the preoperative (or neoadjuvant) setting. Radiotherapy has been used neoadjuvantly for many disease sites, including rectal, pancreatic, esophageal and sarcomatous cancers. Neoadjuvant timing for brain metastases offers several potential benefits. First, target delineation is much simpler preoperatively compared to postoperatively (where the tumor bed is large and can change over time). This smaller treatment volume may also decrease the risk of toxicity or radiation necrosis.

Neoadjuvant radiotherapy may also help with disease control. Local recurrence remain somewhat high (~44%) for tumors greater than 3cm in diameter,[5] likely related to tumor spill at the time of surgery. In addition, there is concern for leptomeningeal spread after surgery due to surgical tract seeding into the meningeal space. Preoperative SRS or SRT to the tumor may serve as a way to, in effect, “sterilize” the tumor site and reduce the risk of local recurrence and leptomeningeal spread. Series have suggested that neoadjuvant SRS or SRT results in lower rates of leptomeningeal disease when compared to postoperative SRS or SRT.[6,7]

The purpose of this study is to prospectively compare preoperative (neoadjuvant) SRS/SRT to postoperative (adjuvant) SRS/SRT in patients undergoing surgical resection for brain metastases.

Hypothesis, Objectives, and Outcomes

We hypothesize that neoadjuvant SRS/SRT prior to surgical resection of brain metastases will result in improved freedom from Central Nervous System (CNS) events when compared to adjuvant SRS/SRT after surgical resection.

Primary Objectives

- Our primary objectives are: (1) to determine the *Time to a Central Nervous System (CNS) Composite Event (CE)* in subjects who receive either neoadjuvant (pre-operative) SRS/SRT or adjuvant (post-operative) SRS/SRT for their brain metastases, and (2) to compare the two treatment arms for evidence of improved Time to a CNS CE among subjects who received neoadjuvant SRS/SRT.
    - A CNS CE will consist of one of the following three events: Local Recurrence (LR) of the treated lesions, symptomatic radiation necrosis (SRN) to the treated lesions, or development of leptomeningeal disease (LMD). See below for detailed definitions of LR, SRN, and LMD.
    - Time to a CNS CE, the primary outcome, will be measured as the time from the date of randomization to the date of a documented LR, SRN, or LMD, whichever occurs first.
    - Death before occurrence of a CNS CE will be treated as a competing risk. Study participants who are alive and have yet to experience a CNS CE at their last evaluation will be right-censored for Time to CNS CE on the date of their last evaluation.

Secondary Objectives related to the Primary Objective. Some of our secondary objectives include (a) determining in each study subject the *secondary outcomes* listed below, and (b) comparing the treatment arms for evidence of improvements in these secondary outcomes.

- Index lesion local recurrence (ILLR), a component of CNS CE, will be defined as the development of new nodular contrast enhancement in the surgical bed compared with the immediate postoperative MRI.
- Non-index lesion LR, also a component of CNS CE, will be defined as an increase of more than 25% in the size of any treated non-resected brain lesion.
    - Time to LR, a secondary outcome, will be measured as the time from the date of randomization to the date of documented occurrence of the LR. Death before occurrence of LR will be treated as a competing risk. Study subjects who are alive and free of LR at their last evaluation will be right-censored for Time to LR on the date of their last evaluation.
- Leptomeningeal disease (LMD), a component of CNS CE, will be diagnosed by imaging results consistent with this condition (either local or diffuse leptomeningeal disease) or by examination of spinal fluid positive for malignant cells.

  - Time to LMD, a secondary outcome, will be measured as the time from the date of randomization to the date of documented first occurrence of the LMD. Death before occurrence of LMD will be treated as a competing risk. Study subjects who are alive and free of LMD at their last evaluation will be right-censored for Time to LMD on the date of their last evaluation.

- Radiation Necrosis (RN) of the treated lesions. If radiation necrosis is suspected based on imaging criteria (progression of contrast-enhancing mass that is associated with reduced perfusion on dynamic MRI, increased T2 flair/T2 hyperintensive signals within previous radiation treatment fields for the index lesion), then follow-up MRI imaging (with MRS, PET/SPECT as optional) will be obtained 4-6 weeks later to confirm the diagnosis of RN. The Time to RN will be back-dated to the initial imaging-findings date if the diagnosis of RN is confirmed by the follow-up imaging.
  - Stratified by surgical site versus non-surgical sites and the use of targeted therapy, cytotoxic chemotherapy, or immunotherapy
- Symptomatic Radiation Necrosis (SRN), a component of CNS CE, will be documented radiation necrosis of the treated lesions (see above) that is accompanied by symptoms (headaches, nausea, vomiting, or other neurologic symptoms).
  - Time to SRN, a secondary outcome, will be measured as the time from the date of randomization to the date of documented occurrence of the SRN. Death before occurrence of the SRN will be treated as a competing risk. Study subjects who are alive and free of SRN at their last evaluation will be right-censored for Time to SRN on the date of their last evaluation.

Other Secondary Objectives include determining the other secondary outcomes described below, and comparing treatment arms for improvements with neoadjuvant SRS/SRT in (a) the rates of secondary yes/no outcomes such as Local Control, or (b) the 6-month, 12-month, 18-month, month rates of secondary time-to-event outcomes such as Duration of Local Control:

- Local Control.
  - Local Control will be defined as Complete Response [CR], Partial Response [PR], or Stable Disease [SD] of the index lesion resulting from the assigned treatment. It will be determined at the first evaluation following successful completion of either neoadjuvant or adjuvant SRS/SRT of all metastatic lesions and surgical resection of the index lesion.
    - Stratified by GTR or STR, piecemeal vs en bloc resection

  - Treatment Failure will be defined either as Progressive Disease [PD] during the assigned treatment, or as the absence of Local Control at the first evaluation following successful completion of the assigned treatment.
  - Duration of Local Control (DLC) will be measured as the time from the date when Local Control is first documented to the date when:
    - the treated lesions show documented evidence of LR or PD, or
    - the patient undergoes whole-brain radiotherapy, repeat SRS, repeat surgical intervention
- Time to distant in-brain failure.
  - Distant in-brain failure (DiBF) will be defined as the occurrence of any new parenchymal lesion outside of the planning target volume.
  - Time to DiBF will be measured as the time from the date of randomization to the date of occurrence of the DiBF. Death before occurrence of DiBF will be treated as a competing risk. Study subjects who are alive and free of DiBF at their last evaluation will be right-censored for Time to DiBF on the date of their last evaluation.
- Overall survival.
  - Overall survival (OS) will be measured as the time from the randomization date to the date of death for any reason. Study participants who are still alive at last follow-up will be right-censored for OS on the date of their last follow-up.
- Time to systemic therapy.
  - Time to initiation or re-initiation of systemic therapy will be measured as the time from the date when the assigned treatment (neoadjuvant versus adjuvant SRS/SRT) is successfully completed to the date when the systemic therapy is initiated or re-initiated.
- Time to subsequent brain treatment, including whole-brain radiotherapy (WBRT), will be measured as the time from the date when the assigned treatment is successfully completed to the date when the WBRT or other subsequent treatment is initiated.
- Radiation/Surgery toxicity
  - The rate of symptomatic (≥grade 2) radiation/surgery toxicity

- Incidence of adverse events as graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Study Design and Procedures

Design: This pilot study is a randomized, open-label, 2-arm active-controlled phase II clinical trial conducted at a single study site (UAMS) located in central Arkansas. Prospective enrollees will be screened based on the inclusion/exclusion criteria listed below in the *Study Population* section. Study-eligible candidates who agree to participate will be assigned by randomization to one of the 2 treatment arms shown in the table below:

Treatment Arm	Intervention/treatment
Experimental: Arm I (pre-operative SRS/SRT) Patients undergo SRS or SRT within 15 days of randomization followed by surgery within 15 days of radiation completion. Patients may undergo additional SRS or SRT if disease returns after treatment.	Radiation: Stereotactic Radiosurgery Undergo SRS/SRT Other Names: • Stereotactic External Beam Irradiation • stereotactic external-beam radiation therapy • stereotactic radiation therapy • Stereotactic Radiotherapy • stereotaxic radiation therapy • stereotaxic radiosurgery
Active Comparator: Arm II (post-operative SRS/SRT) Patients undergo surgery within 15 days of randomization followed by standard-of-care SRS or SRT within 30 days of surgery. Patients may undergo additional SRS or SRT if disease returns after treatment.	Undergo SRS/SRT Other Names: • Stereotactic External Beam Irradiation • stereotactic external-beam radiation therapy • stereotactic radiation therapy • Stereotactic Radiotherapy • stereotaxic radiation therapy • stereotaxic radiosurgery

The dose, volume and fractionation of radiotherapy will be at the discretion of the radiation oncologist at the time of SRS/SRT depending on the size, location, and proximity to critical structures. Before treatment commences, each study participant will be stratified according to two stratification factors:

- Size of Index Lesion (<3 cm versus ≥3 cm)
- Number of Brain Metastases (4 or fewer versus 5 or more)

These stratification factors will be used during the randomization procedure to assure that the treatment arms will be well-balanced with respect to index-lesion size and brain-metastasis number.

On-study Plan: After first signing the IRB-approved Informed Consent form, and after then being stratified according to size of index lesion and number of brain metastases, study participants will be registered and assigned a study number by a clinical research associate (CRA) or Study Coordinator.

Randomization and Treatment Allocation: After the study participant's eligibility has been confirmed, and after the participant has been stratified (see above) and registered in the Research Participant Registration System (RPRS), the study coordinator will do two things. First, the study coordinator will use the RPRS to assign the participant to one of the four possible strata defined by the stratification factors. Then the study coordinator will use the RPRS to randomize the participant in a 1:1 allocation ratio to either Arm I (pre-operative SRS/SRT) or Arm II (post-operative SRS/SRT). The randomizations will be balanced 1:1 on treatment arms within each stratum by using a permuted-blocks approach. Study participants will receive either pre-operative or post-operative SRS/SRT depending on the study arm to which they are randomized. Accordingly the two study arms will follow the treatment schedules shown in the table.

Sample Collection: The extent (gross total or subtotal resection) and technique for surgery (en bloc or piecemeal) will be determined by the neurosurgeon. The pathological specimen will be analyzed and stored by the Department Pathology per standard operating procedure for resected brain tumor specimens.

Follow-up: After completion of radiotherapy and surgery, study subjects will be followed by Brain MRI every 2-3 months for the first year and then every 4-6 months indefinitely (in accordance with National Comprehensive Cancer Network [NCCN] guidelines). Imaging and follow-up can be done sooner than these specified times if clinically indicated. MRI's will be included in study results up to 18 months.

Study Population

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No
Estimated Enrollment	104 (we anticipate consenting 120 in order to reach this goal)

Inclusion Criteria

- Patients with prior histopathological diagnosis of cancer other than small cell lung cancer, lymphoma, and germ cell histologies.
- MR imaging of the brain with findings strongly suggestive of metastatic tumor(s) as assessed by the radiologist.
- Seen by a neurosurgeon or radiation oncologist and judged to be appropriate for participation in this study, including the ability to tolerate both surgery and SRS/SRT, e.g., the ability to lie flat in a stereotactic soft head frame.
- ECOG ≤ 2
- 1-2 index lesion(s) appropriate for resection, not previously treated with SRS/SRT. Index lesion(s) should be ≥ 1.5 cm and < 5 cm in largest dimension, and require resection. Alternatively, patients with a diagnosis of melanoma and a lesion < 1.5cm in largest dimension may also be included.
    - All other brain lesions must be appropriate for SRS/SRT alone and treated according to physician preference. Prior neurosurgery and/or prior SRS/SRT at a non-overlapping location are permitted at the discretion of the treating physician.
- MRI confirmed 1-10 lesions, 1-2 of which are the index lesions undergoing surgery. Each non-index lesion (up to 10) must measure ≤ 3.0 cm in maximal extent on contrasted MRI scan, and not otherwise require resection.
- Clinical indication and plan for stereotactic radiosurgery to all known brain lesions requiring treatment (≤ 10 metastases).
- Surgical resection able to be performed within 15 days of radiotherapy completion.
- Written informed consent obtained from subject, or a legally designated power of attorney and ability for subject to comply with the requirements of the study.
- Negative pregnancy test in women of childbearing potential (WOCBP) within 30 days of radiation. WOCBP is a female patient less than 50 years of age or who has menstruated within the last 12 months.
- Platelet count > 80 k/cumm, Hgb > 7.5 gm/dL, INR < 1.3, ANC > 1.5 k/cumm

Exclusion Criteria

- Not a surgical candidate per neurosurgeon's discretion.
- Contraindication to general anesthesia.
- Not a radiosurgical candidate per radiation oncologist's discretion.
- Metastatic germ cell tumor, small cell carcinoma, leukemia, multiple myeloma or lymphoma or any primary brain tumor
- ECOG > 2
- < 3 months expected survival
- Radiologic documentation of hydrocephalus in addition to symptoms of hydrocephalus
- Radiographic or cytologic evidence of leptomeningeal disease.
- Imaging Findings:

  - Midline shift > 6mm
  - >10 lesions, one of which is the index lesion
  - Largest lesion > 5cm
- Pregnancy
- Known allergy to gadolinium, pacemaker, or other contraindication such as metal implant that is not safe for MRI. Patients with MRI-compatible implants are eligible.
- Patients who have local recurrence of previously treated brain metastasis.
- Patients who have received prior WBRT.
- Inherited radiation hypersensitivity syndromes
  - Ataxia Telangiectasia, Nijmegen Breakage Syndrome, Fanconi Anemia, DNA Ligase IV, Mre 11 deficiency, SCID, Bloom's syndrome
- Collagen vascular diseases
  - Active systemic lupus erythematous (SLE), scleroderma, mixed connective tissue disorder, polymyositis or dermatomyositis, CREST Syndrome
- Cytotoxic Chemotherapy within 7 days prior to SRS/SRT.
  - Molecularly targeted therapies, including immune-modulatory drugs, can be given within 7 days of SRS/SRT at the discretion of the treating physician.
- Patients who received anti-VEGF therapy within 6 weeks prior to enrollment, as there is increased risk of fatal brain hemorrhage with surgical resection.
- Treatment plan respecting normal tissue tolerances using dose fractionation specified within the protocol cannot be achieved.

Risks and Benefits

Potential risks

A risk to study participants is the potential for loss of confidentiality of study data. Measures to protect the confidentiality of study data will be implemented as described in the Data Handling and Recordkeeping section below.

A risk to study participants is that pathologic confirmation of target lesion is not available. There is a possibility that a lesion (that is radiologically/clinically consistent with a brain metastasis) may represent an infectious/inflammatory process or a separate malignancy. In that case, neoadjuvant SRS/SRT may not represent the optimal treatment option. This risk is being minimized by only including patients with biopsy proven malignancies (where the biopsy was performed at the primary cancer site or another metastatic site) but there is still a small risk that the target lesion may represent an infectious/inflammatory process or a separate malignancy. However, this risk is not greater than the standard of care for brain metastases diagnosed by radiographic imaging or clinical findings, as these patients may receive surgery and/or radiation of the target lesion without pathologic confirmation.

A risk to study participants is the increased risk of delayed wound healing with neoadjuvant SRS/SRT compared to adjuvant SRS/SRT.

Potential benefits

A potential benefit to study participants is the potential improved target delineation with neoadjuvant SRS/SRT. Since the tumor bed can change over time, adjuvant SRS/SRT involves challenges in delineating the target volume of a dynamically changing target, which may lead to geographic miss and increased radiation dose to normal tissues. Improved target delineation with neoadjuvant SRS/SRT may potentially improve local control and reduce toxicity.

A potential benefit to study participants is a potential reduction in the rates of radiation necrosis. With neoadjuvant SRS/SRT, the tumor and adjacent normal tissue that has been irradiated is removed at the time of surgery, reducing the availability of injured tissue and inflammatory reaction needed to precipitate radiation necrosis. In contrast, for adjuvant SRS/SRT, the irradiated tissue remains. Retrospective data suggests the rate of symptomatic radiation necrosis is lower with neoadjuvant SRS/SRT compared to adjuvant SRS/SRT.[6]

A potential benefit to study participants is a potential reduction in the rates of leptomeningeal disease. With neoadjuvant SRS/SRT, the tumor site is “sterilized” and the risk of leptomeningeal disease may be minimized even with tumor spill, as tumor cells may be replicatively dead. Retrospective data suggests the rate of symptomatic radiation necrosis is lower with neoadjuvant SRS/SRT compared to adjuvant SRS/SRT.[6]

A potential benefit to study participants is potential immune system activation against tumor cells. Radiotherapy to an intact tumor may allow for increased immune activation and in situ vaccination, allowing for greater immune response against the tumor cells. Animal models have suggested this benefit but it is not well-studied in human subjects.[8]

Finally, knowledge gained from the study could potentially benefit patients in the future.

Data Handling and Recordkeeping

The Principal Investigators will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study.

Information will be coded with the key to the code kept separately. Data will be stored securely on UAMS-maintained computers and servers. Only investigators listed on this protocol will have direct access to patient-identifying data. Research assistants, coordinators, and statisticians will only have access to coded data. At the conclusion of the study, the coded data will be de-identified.

Data Safety Monitoring Plan: The study will be monitored by the investigators to ensure that the rights and well-being of human subjects are protected, that the data are accurate, complete and verifiable from source documents and that the trial is conducted in compliance with currently approved protocol/amendments. The PI and sub-Investigators will review study conduct on an ongoing basis. The PI will assure that all protocol deviations, AEs, and SAEs are reported to the IRB according to the applicable regulatory requirements.

Specimen Handling and Storage

Tumor specimens will be collected from surgical resection and stored by the Department of Pathology and kept as part of standard of care. No samples will be collected specifically for use in this study at this time.

Data Analysis

Statistical analysis plan

Patient characteristics will include patient demographics, disease characteristics of the primary tumor, and relevant characteristics (number, location, size, etc.) of the brain metastases being treated. Patient characteristics will be summarized by treatment arm with medians, quartiles, and ranges for numeric characteristics, or with numbers and percentages for category characteristics. Each characteristic then will be assessed for imbalance between treatment arms with Wilcoxon's rank-sum test for numeric characteristics and the chi-square test for category characteristics. The imbalance assessments will consist of 2-sided tests that employ the standard $\alpha=0.05$ significance level.

Time to a CNS CE, the primary outcome, will be visualized with Cumulative Incidence (CI) curves computed using Kaplan-Meier methodology, summarized by treatment group as CI proportions at 6, 12, and 18 months, and compared for difference using the Fine and Gray model for equality of CI functions when death before a CNS CE is treated as a competing risk. Times to each of the individual CNS events (LR, SRN, LMD, DiBF, and WBRT) will be analyzed the same way, except that each Fine and Gray model will have the competing risk be death before the individual event being analyzed. Overall survival will be visualized using standard Kaplan-Meier curves and compared for differences via the log-rank test. Because this is a pilot study, all time-to-event outcomes will be compared for evidence of improvement on the pre-operative SRS/SRT arm using 1-sided tests that employ an $\alpha=0.10$ significance level.

Sample size, power, and study duration

Sample-size calculations are informed by results from Patel et al.'s retrospective study.[6] Based on their results, we expect that the post-operative SRS/SRT arm will have an average CNS CE rate of approximately 25% per year, accompanied by an average competing-risks rate of approximately 32% per year (where the competing risk is death before the CNS CE). Sample-size calculations are also informed by the fact that UAMS typically sees approximately 50 patients per year who should meet this study's eligibility requirements.

To meet its objectives, our randomized Phase II pilot study of pre-operative SRS/SRT versus post-operative SRS/SRT needs to have >80% power to detect a 50% decrease in the rate of CNS CE on the pre-operative SRS/SRT arm using a 1-sided test at 10% alpha. The power of tests under the Fine and Gray competing-risks model is well-approximated by the power of log-rank tests calculated with the competing-risk rate represented as non-zero dropout rates on each study arm. To calculate power of 1-sided log-rank tests at 10% alpha, we implement the following assumptions in PASS 16 software[9]:

- Accrual duration will be three years while minimum follow-up will be 1.5 years, leading to a total study duration of 4.5 years.
- The post-operative SRS/SRT arm will have a CNS CE rate that averages 25.0% per year.
- The pre-operative SRS/SRT arm will have a CNS CE rate that averages 12.5% per year, or half the rate on the post-operative SRS/SRT arm.
- Both arms will have a dropout rate of 32% per year due to the competing risk.
- The crossover rate from one arm to the other will be zero on both arms.
- Sample sizes will be equal on both arms.

Under these assumptions, a sample size of 52 subjects per treatment arm (a total of 104 subjects) is calculated to provide the 1-sided log-rank test (and thus the equivalent Fine and Gray test) with 80.7% power at 10% alpha to detect a 50% reduction in the CNS CE rate with pre-operative SRS/SRT relative to the CNS CE rate with post-operative SRS/SRT. Under the same assumptions, the number of CNS CE's is projected to reach expected values of 8.6 with pre-operative SRS/SRT and 17.4 with post-operative SRS/SRT for a total expected value of 26.0 by the end of the study.

Recruiting the required study total of 104 subjects over the 3-year accrual duration leads to a recruitment rate of 35 subjects per year. Given that UAMS typically sees approximately 50 study-eligible patients per year, a recruitment rate of 35 subjects/year represents a recruitment-success rate of 70%. We consider 70% to be a feasible recruitment-success rate.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject or legally authorized representative and the person obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in the research record.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant. The study will be listed on clinicaltrials.gov in accordance with (journal or FDA) requirements.

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