# UCSD Image-Guided Cognitive-Sparing Radiosurgery for Intracranial Lesions: Avoidance of Eloquent White Matter and Hippocampal Regions

NCT04343157

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Study Protocol

**UCSD Human Research Protections Program**
**New Biomedical Application**
**RESEARCH PLAN**

## 1. PROJECT TITLE
UCSD IIT – Image Guided Cognitive Sparing Intracranial Stereotactic Radiosurgery (COG-SRS)

## 2. PRINCIPAL INVESTIGATOR
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Professor; Chief, Central Nervous System Tumor Service
Department: Radiation Medicine and Applied Sciences

## 3. FACILITIES
The study will be performed at the following sites:

- UCSD Moores Cancer Center, 3855 Health Sciences Dr, La Jolla, CA 92093
- UCSD Center for Translational Imaging and Precision Medicine (CTIPM), 9427 Health Sciences Drive, San Diego, CA 92093
- UCSD Medical Center - Hillcrest, 200 West Arbor Dr, San Diego, CA 92103
- UCSD Medical Center - La Jolla (Jacobs Medical Center), 9300 Campus Point Dr, La Jolla, CA 92037
- UCSD Medical Center - Vista, 910 Sycamore Street, Suite 102, Vista, CA 92081 (recruitment purposes only)
- UCSD Medical Center - Encinitas, 1200 Garden View Road, Suite 200, Encinitas, CA 92024 (recruitment purposes only)

## 4. ESTIMATED DURATION OF THE STUDY
The estimated duration of this study is 10 years.

## 5. LAY LANGUAGE SUMMARY OR SYNOPSIS
The purpose of this study is to understand whether advanced brain imaging (BOLD-fMRI and DTI) can be incorporated into the design of radiation therapy in a way that will help spare critical brain regions from high doses of radiation in patients with brain lesions. This study will also determine whether this type of radiation sparing results in improvements in the patient's thinking relative to individuals who did not receive this approach (from published data). This will be determined by tracking predetermined biomarkers and by associating these with measures of thinking ability.

## 6. OUTCOMES AND ASSESSMENTS

### Primary Outcome
The primary outcome is functional preservation at 3 months, assessed by neuropsychological testing across memory, language, executive function, attention/processing speed, and fine motor control. Raw neuropsychological test scores are converted to standardized T-scores using published normative data. Domain scores are calculated as the mean T-score of tests assigned to each domain.

### Secondary Outcomes
- Mood and health-related quality of life at baseline and 3 months.

- Local control of treated lesions on serial MRI.
- Distant intracranial failure, defined as any new intracranial lesion outside the treated SRS planning target volume.
- Overall survival, measured from SRS to death from any cause.
- Radiographic radionecrosis on serial brain MRI.
- MRI biomarkers of radiation-associated white matter injury, including fractional anisotropy change from baseline to 3 months within connectome white matter voxels.

Local control of brain metastases is assessed using Response Assessment in Neuro-Oncology Brain Metastases criteria. Meningioma progression is defined as a 25% or greater increase in size relative to posttreatment nadir. All available follow-up imaging is reviewed to distinguish true progression from transient posttreatment enlargement that later stabilizes or regresses.

## 7. BACKGROUND AND SIGNIFICANCE

Each year, approximately 100,000 cancer patients will develop brain metastases, and over 20,000 new benign brain tumors will be diagnosed[4]. Given that most systemic therapies do not penetrate the blood-brain barrier, radiation therapy (RT) including intracranial stereotactic radiosurgery (SRS) is a mainstay of treatment for these patients. However, RT is limited by damage caused to healthy brain tissue, with corresponding neurocognitive decline seen in most patients that survive longer than 6 months[5]. RT-induced cognitive impairment is the single most common complication of long-term survivors. Late delayed effects include decreases in verbal and nonverbal memory, executive functioning, language functioning, among other deficits, and can be devastating for patients. However, cognitive deficits experienced by these patients are highly variable and depend on the location of the tumor itself, as well as the dose and location of radiation. Thus, efforts to avoid cognitive decline must be aimed at sparing critical brain regions (i.e., eloquent brain) from high doses of RT.

Intracranial stereotactic radiosurgery (SRS) uses high, ablative doses of radiotherapy directed at the tumor or lesion, with no regard for critical white matter or cortical structures in standard-of-care. Rational design of cognitive-sparing SRS must be informed by a detailed clinical and neuroanatomic understanding of cognitive function. Currently in radiation planning, there is little attention paid to the functional importance of different white matter tracts and cortical regions involved in the regulation and control of important cognitive processes. With the advent of advanced, quantitative imaging and automated methods for reconstructing fiber tracts and delineating eloquent cortex, it is now possible to obtain this information in a clinically feasible and efficient manner for treatment planning. Such methods have revolutionized neurosurgical planning[6-9] but have only sparsely been applied to RT planning (see below).

<u>BOLD-FMRI and DTI to reduce motor complications in RT planning.</u>

To date, only a few RT studies have used BOLD-FMRI and DTI in RT planning. One previous study utilizing DTI of the corticospinal tract (white matter bundle critical for motor functioning) in RT planning showed reduced motor complications in a retrospective cohort [10]. A similar study in high-grade glioma patients found that relative sparing of the primary motor cortex and corticospinal tract was feasible using BOLD-fMRI and DTI[11]. A retrospective DTI study correlated high RT doses to the arcuate fasciculus with symptomatic aphasia in 12 patients with brain lesions [9]. Despite these initial studies, there are no prospective data on the use of BOLD-fMRI and DTI for sparing of critical white matter and cortical regions in SRS with cognitive outcomes. We contend that sparing eloquent and critical brain regions and structures could greatly mitigate the cognitive effects of radiation injury in many patients with brain lesions.

## 8. PROGRESS REPORT/PRELIMINARY STUDIES

Not applicable.

## 9. RESEARCH DESIGN AND METHODS

**Participants:** We will prospectively enroll approximately 80 patients who will be undergoing intracranial SRS (fractionated partial brain radiotherapy or stereotactic radiosurgery to the brain) at UCSD/MCC. Study subjects will include those with benign lesions (meningiomas, arteriovenous malformations) for whom intracranial SRS is indicated as well as malignant lesions with expected prognosis >6 months (based on systemic disease burden, age, histology, number of metastatic sites in the brain). This is feasible given that approximately 150 patients are treated at UCSD/MCC yearly that meet our eligibility criteria. Inclusion criteria include: age >18, Karnofsky performance status ≥70, ability to answer questions and follow commands, estimated life expectancy > 6 months. Patients must be able to undergo MRI otherwise they will be excluded.

Study patients will undergo neuropsychological testing, DTI (and BOLD-fMRI for patients with AV Malformations) prior to SRS, receive cognitive-sparing SRS, and then be followed with standard MRI sequences to evaluate for tumor control approximately every 2-3 months, as clinically indicated thereafter (current standard of care). Patients with AV Malformations will only get an MRI at approximately 3 months post-RT, when clinically indicated, since they are not malignant. At approximately 3 months post-RT, cognitive testing will be repeated. We will compare the cognitive scores in our cognitive-sparing SRS study to the standard SRS only arm of the Alliance randomized trial[1]. Cognitive outcomes and scores at progressive time points are published and available[1].

**Neuropsychological data**: A battery of cognitive tests will be performed prior to RT and at-approximately 3 months post-radiation, as shown in the table below. This testing evaluates the domains of attention/processing speed, executive function, language, memory, and fine motor control. Testing will be performed by trained personnel under neuropsychological supervision. When in-person testing is not feasible, remote testing may be used for measures suitable for remote administration; unavailable metrics that require in-person assessment are documented as missing.

| Cognitive Domain | Neuropsychological Tests |
|---|---|
| Language | Boston Naming Test<br>D-KEFS Verbal Fluency |
| Memory | Hopkins Verbal Learning Test–Revised |
| Attention/Processing Speed | Trail Making Test–Part A<br>WAIS Digit Span Forward, Total |
| Executive Functioning | Trail Making Test–Part B<br>WAIS Digit Span Backward, Sequencing |
| Fine Motor Testing | Grooved Pegboard Dominant, Non-dominant |

**Neuroimaging:** All MRI scans for this clinical trial will be performed on a GE Discovery MR750 3T MRI scanner at the UCSD Center for Translational Imaging and Precision Medicine (CTIPM). Imaging will be added on to the current standard-of-care imaging all SRS patients undergo for radiation planning. All imaging analysis will be performed at the UCSD Center for Multimodal Imaging and Genetics (CMIG). Post-treatment imaging will be acquired with standard of care

MRIs at approximately 2-3 month intervals, as clinically indicated, to evaluate lesion/tumor control up to 1 year post-RT. Imaging biomarkers of radiation-induced change in white matter, cortex and the hippocampus will be analyzed according to procedures described in Seibert et al.[12]. All MR images will be corrected for geometric distortions before coregistration of the MRI to CT simulation. Registration will be confirmed visually slice by slice, and the resulting transformation matrix will be used to resample the delivered radiation dose distribution from the treatment plan to the MRI space. FreeSurfer software (http://surfer.nmr.harvard.edu, version 7.1) or FastSurfer (version 2.4) software will be used to reconstruct the cortical surface from each T1-weighted MRI volume, weighted by T2-weighted FLAIR to correct for edema or hypointensity. This same process will be used to segment subcortical white matter structures and hippocampal volumes. Each case will be reviewed visually in a meticulous, slice-by-slice basis to identify errors in the automated estimates. Tumor beds and surgical changes will be manually censored from analyses as they can contribute to errors in segmentation.

*DTI acquisition, processing, and tractography*. Diffusion data will be acquired using a single-shot pulsed-field gradient spin-echo EPI sequence (TR=96ms; FOV= 240mm, matrix=96x96x48) with 4 b-values ($b$=0, 500, 1500, and 4000 s/mm$^2$), and 6, 6, and 15 unique diffusion directions. All data will be corrected for distortions due to susceptibility, gradient nonlinearities, eddy currents, and motion[1314] *Tractography*: Fiber tracts will be reconstructed using a probabilistic diffusion tensor atlas that was developed in our lab at CMIG (i.e., AtlasTrack)[15]. This method is a fully automated method for labeling fiber tracts in individual subjects based on diffusion weighted images, T1-weighted images, and a probabilistic atlas of fiber tract locations and orientations. AtlasTrack will be used to segment the individual white matter tracts of the cognitive connectome, including 10 bilateral white matter tracts and the corpus callosum.

*FMRI acquisition, processing, and analysis.* BOLD images will be acquired using a T2*-weighted EPI sequence (TR=3000ms, TE=30ms; flip angle 90°; 3.4x3.4x2mm voxels; FOV=220mm). Geometric distortions caused by susceptibility artifacts will be minimized using paired images with opposite phase-encoding polarities[16]. FMRI analysis will be performed using Analysis of Functional NeuroImages (AFNI)[17].

*Language, memory, motor, executive functioning mapping.* Patients will perform directed tasks of language (i.e., word reading), memory, motor functioning, or executive functioning (task-switching), which are well-validated for pre-surgical brain mapping in patients[18, 19] Each task takes approximately 4-8 minutes to complete. Performance accuracy will be monitored throughout the scan session by having patients respond with a MRI-safe button box.

*Task analysis*: General Linear Modeling (GLM) will be performed using AFNI's 3dDeconvolve and GLM contrasts between the condition of interest (e.g., language) and control task will be calculated. Contrast estimates will be projected to the cortical surface after fMRI data are registered to $T_1$-weighted MRIs using the joint probability distribution function method[20] with coarse pre-alignment based on within-modality registration to atlas brains. FMRI and DTI data will then be co-registered in 3D space (see Figure below).

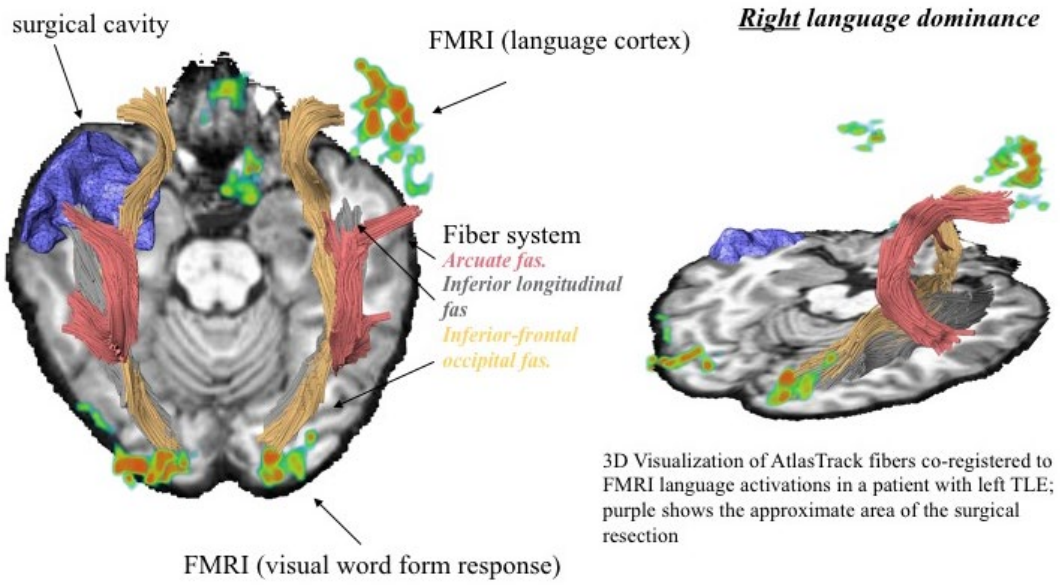



Figure. Co-registration of DTI tractography and language fMRI activations in a patient with a left temporal lobe lesion.

**Radiation Planning:** DTI tractography (and BOLD-fMRI maps when available) will be imported into the Eclipse™ RT planning system and co-registered with planning CT scans for each patient. All imaging data will be visually inspected to ensure proper segmentation. Standard tumor/target volumes and critical structures (brainstem, optic chiasm and nerves, globes, spinal cord) will be delineated per standard of care. Each case will be planned using volume modulated arc therapy/intensity modulated SRS, and optimized within our standard clinical guidelines with the addition of critical white matter and cortical regions of avoidance[21]. Prescription dose and number of fractions (treatments) to the target lesion will be chosen by the treating radiation oncologist depending on the case; for intracranial SRS, this clinical decision is based on target/tumor size and volume, proximity to critical structures, and histology (benign or malignant). Stereotactic radiosurgery plans will be optimized to keep critical cortical and white matter regions LOWER than standard of care SRS plans: max dose <12Gy in single fraction SRS, with constraints for 3- and 5-fraction SRS derived from this single fraction equivalent. Max dose is equivalent to dose to 0.03cc of the volume of that structure. All plans will ensure 98% of the PTV is receiving 100% of the prescription dose[9, 10]. Dose volume histograms will be assessed and re-optimized if necessary, without compromising coverage of tumor or sparing of standard critical structures. In cases where it is not possible to spare the identified cognitive areas per the above guidelines, the lowest possible doses to these regions will be chosen.

**Statistical Considerations:**

**Primary Objective Analyses:** Cognitive test results obtained at baseline and 3 months after SRS are scored using standardized published normative data. Raw scores are converted to age-, sex- and education-adjusted T-scores as available. Tests are grouped into cognitive domains, and domain scores are calculated as the mean T-score of all tests associated with that domain. The primary analysis evaluates change in domain-level cognitive performance from baseline to 3 months after SRS. Linear mixed-effects models will be used to estimate mean T-

score change within each domain. Covariates include age, number of lesions, steroid use, anti-seizure medication use, prior intracranial surgery, and systemic therapy.

**Historical Control Comparison:** For the historical control comparison, cognitive outcomes in the brain metastases subset will be compared with historical controls treated with standard SRS on Alliance N0574 and N107C. Deidentified raw test scores are obtained from the National Cancer Institute National Clinical Trials Network Data Archive and the Alliance Cooperative Group. Scores will be standardized using pooled test means and SDs across all trials, and domain-level scores will be calculated as the mean of associated tests common to all datasets. Analyses include patients with at least one baseline and 3-month test pair. Domain-specific mixed-effects models will fit 3-month domain score as the outcome and trial group as the primary predictor. Models adjust for baseline score, age, sex, race, ethnicity, and number of brain metastases.

**Secondary Objective Analyses:**

- Mood and health-related quality-of-life total and subscale scores will be evaluated among patients with paired baseline and 3-month assessments using Wilcoxon signed-rank tests.
- Time-to-event endpoints will be summarized using Kaplan-Meier methods. Radiographic radionecrosis is evaluated on serial MRI.
- Fractional anisotropy maps are derived from diffusion MRI at baseline and 3 months. FA change will be summarized in two bins: below or above the white matter dose threshold.

**Sample Size Determination**

With planned enrollment of 80 patients and an expected attrition rate of 25%, approximately 60 evaluable patients were expected to contribute paired baseline and 3-month cognitive data. The historical-control comparison was planned using evaluable patient-level data from the SRS arms of Alliance N0574 and N107C, with an expected historical-control sample size of approximately 129 patients. As the comparative cognitive analysis uses standardized Z scores, the detectable effect is expressed as a standardized between-group difference in 3-month cognitive performance. Assuming 68 evaluable COG-SRS patients, 129 evaluable historical SRS controls, 80% power, an alpha of 0.05, and a baseline-to-3-month correlation of 0.7, the study was expected to detect a standardized between-group difference of approximately 0.3 SD. The final comparative analysis will adjust for baseline cognitive performance and covariates available across datasets.

## 10. HUMAN SUBJECTS

Expected accrual at UCSD is approximately 80 subjects in this single-center study. Study subjects will include those with benign lesions (i.e. meningiomas, AVMs) for whom brain SRS is indicated, and among whom survival expected to be many years. For brain met patients, prognosis can certainly be >6 months depending on other factors (i.e. systemic disease burden, age, histology, number of metastatic sites in the brain). Selection criteria will include evaluation of these factors.

Patients will be eligible for participation if they have a need for intracranial SRS. Inclusion criteria include: age >18, Karnofsky performance status ≥70, ability to answer questions and follow commands, estimated life expectancy > 6 months, ability to undergo MRI.

Patients who received prior radiation in the same vicinity as the lesion to be spared would be excluded.

Patients will not be excluded on the basis of gender or ethnicity.

Pregnant persons and prisoners will be excluded.

**11. RECRUITMENT**

Subjects will include those patients seen at a facility in the UCSD Health System. Information regarding the study will be included on the Moores UCSD Cancer Center Clinical Trials webpage and the American Cancer Society Clinical Trials Matching Service online.

For those patients under the clinical management of the recruiting investigator, the investigator will review the patient's medical records and determine if they would be a candidate for the study. The investigator will approach the subject and offer participation in the trial.

Prospective study subjects who are employees of UCSD will not be directly (one-on-one) pursued for study participation. They will not be contacted via direct supervisors for enrollment. There are no direct reports to the designated Study Coordinator.

Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent.

Pre-screening Process of Subjects outside the Clinical Management of Recruiting Investigator

Recruitment procedures will also involve the review of subject records by designated study personnel (e.g., investigators and/or study coordinators) in order to identify potentially eligible subjects. Since Protected Health Information (PHI) will be accessed via the hospital's medical record database and scheduling system (e.g., EPIC/IDX) *prior* to contacting the potential subject about the research study, we are requesting a ***partial*** waiver of HIPAA authorization for access to PHI for purposes of prescreening only.

The investigator believes this study meets the following requirements for this request per 45 CFR 164. 512(i)(2)(ii):

1. The use or disclosure of protected health information (PHI) involves no more than minimal risk to the privacy of individuals as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out.
2. Granting of the waiver will not adversely affect privacy rights and welfare of the individuals whose records will be used as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out.
3. The pre-screening could not practicably be conducted without a waiver because we need to search project the EPIC electronic database to identify eligible subjects.
4. The project could not practicably be conducted without use of PHI because demographic and clinic information are needed in order to identify eligible subjects.
5. The privacy risks are low relative to the anticipated benefits of research. The privacy risks are minimal since all reasonable efforts to protect confidentiality will be performed and there is the potential to gain scientific knowledge that will benefit future cancer patients.
6. An adequate plan to protect identifiers from improper use and disclosure is included in this research proposal. See Items 15 and 16.
7. An adequate plan to destroy the identifiers at the earliest opportunity is included in the research proposal. See Item 16.

8. The PHI will not be re-used or disclosed for other purposes.

Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent.

If the treating physician agrees with the prescreening plan, the prescreener will obtain permission from the treating physician for prescreening of their subjects' medical records before those records are reviewed by any study personnel. A brief subset of preliminary eligibility criteria such as age, gender, diagnosis, stage, prior treatment, will be reviewed by study personnel to determine subjects' preliminary eligibility for the research study. No written record of this information will be created. There will be no direct contact of the potential research subject by the prescreener (i.e., study staff). The prescreener will then ask the subject's treating physician to approach the subject. The treating physician will further discuss the research study with the potential subject and ask whether they would like to be contacted by study staff to discuss the trial (i.e., counseling) and/or provide the potential subject with the study staff's contact information. Eligibility may be formally determined at the time of counseling, but any research-specific screening procedures will only be performed after informed consent is obtained and a standard, stand-alone HIPAA authorization form is signed.

For the purposes of pre-screening ONLY: A request for ***partial*** waiver of consent is requested. The investigator believes the pre-screening to be used for recruitment in this study meets the following requirements for this request per 45 CFR 46.116:

1. The (pre-screening) research involves no more than minimal risk to the subjects as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects used as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out;
3. The (pre-screening) research could not practicably be carried out without the waiver or alteration as the research staff needs to search the EPIC electronic database to identify eligible subjects; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Clinical Trials Navigator

The Clinical Trials Office will employ a Clinical Trials Navigator (CTN) to assist with the navigation and/or recruitment of patients to clinical trials. The CTN will have a working knowledge of the protocol eligibility requirements and enrollment opportunities for trials available through the CTO.

The CTN will access patient medical records facilitating the above detailed pre-screening process, act as contact for subject referrals from patients or investigators, and will be listed as the clinicaltrials.gov primary contact for investigator-initiated trials.

Other Recruitment Methods

Recruitment methods may include presenting the basic trial information as detailed below in a written format (e-mail, flyer, or letter) to the research and/or clinical staff of MCC, presentation at Disease Team Meetings, presentation at MCC Tumor Boards, and postings in e-mailed newsletters such as Delivering Discoveries.

1. The title; purpose of the study;

2. Protocol summary;
3. Basic eligibility criteria;
4. Study site location(s); and
5. How to contact the site for further information.

**12. INFORMED CONSENT**

Subjects will be asked to provide written consent, using an IRB-approved consent form. The consent process will take place prior to performing any study related procedures and in a private location or through secure video conferencing via programs like EPIC and Zoom. The use of DocuSign Life Sciences for electronic signatures will be utilized for remote consents. The Investigator or study coordinator will describe the study, including detailed information about risks and benefits, to potential subjects. The investigator or study coordinator will provide potential subjects with an IRB-approved consent form. Subjects will be given ample time to read this consent form at the same visit or may take it with them to read at another time. Potential study subjects will be given the opportunity to ask and receive answers to all questions they may have about the study, its risks and benefits, or the consent form itself before signing the consent form. As this research is subject to HIPAA privacy rule provisions, participants will also be requested to sign a separate authorization for the use of protected health information (i.e., HIPAA form specific to the research study). The investigator or study coordinator will obtain informed consent in a language understood by the prospective study candidate using certified translations of study documents and qualified translators, where applicable.

No UCSD employee shall be directly (one-on-one) recruited, nor consented by an individual to whom they report directly or who is in the chain of command about them. The consent process shall be performed by a peer or someone lower in the team hierarchy than the participant in order to mitigate any possible coercion presented by power differential between consenter and consented. There will be no penalty to the employee for declining consent.

Subjects who fulfill the eligibility criteria will be offered further participation in this study. Only subjects who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log.

A copy of the signed informed consent and assent (when applicable) forms and HIPAA authorization will be placed in the research subject's medical record. The original consent form and HIPAA authorization will be retained in the master research file.

A copy of the HIPAA authorization and informed consent form(s) that will be used on this study are attached to this IRB application for review.

**13. ALTERNATIVES TO STUDY PARTICIPATION**

Other therapeutic alternatives for this subject population may include other chemotherapy or chemotherapy combinations, other targeted therapies, or other investigational drug(s). The subject may also seek palliative (supportive) care alone or in addition to study treatment.

**14. POTENTIAL RISKS**

The anticipated risk to patients in this study is minimal.

Intracranial SRS would be performed identically to standard of care, except for adding additional regional avoidance for cognitive sparing. In cases where sparing of these structures cannot be

performed without sacrificing treatment of the target or another critical structure, this will be recorded and the default will be the standard clinical plan. While clinical benchmarks of SRS quality will not be sacrificed on this study, there is a possibility that changing the SRS plan to achieve cognitive sparing may change the dose distribution to other structures in the brain. It is unclear whether this would change any clinical outcomes since SRS plans must adhere to the same rigorous standards as the current standard of care.

***Risks of Intracranial Stereotactic Radiosurgery (SRS):***
Like all other cancer treatments, there are risks for subjects who undergo radiation therapy. Radiation used to damage or destroy cancer cells/tumor cells may also hurt normal cells. When this happens the subject may experience side effects. The risk of side effects outweighs the potential benefits. The targeting physician will have explained this in detail to any subject undergoing radiation therapy.
Participants in this protocol will undergo radiation therapy with stereotactic radiosurgery (also known as SRS). The treating physician will select the appropriate dose and number of treatments based on the participant's condition and disease process, as per standard of care. Examples include 1 to 5 total SRS treatments, with doses varying from 12-40Gy.

The side effects from SRS will depend on the patient's diagnosis, target region to be treated, other therapies they may be receiving, and pre-existing health conditions. These will have been discussed in detail by the treating physician with the patient in their clinical consultation, and these side effects are documented on the treatment consent form. Participation in this study should not alter or change the expected side effects, other than the hypothesis being tested that cognitive-sparing SRS may reduce cognitive side effects. Some side effects associated with intracranial SRS include: fatigue, mild skin irritation, hair loss in the area of treatment. Other possible, but less common, side effects include headache or worsening of pre-existing condition or neurological symptoms from inflammation around the target area. Possible long term side effects include effects on cognitive (thinking) function, which this clinical trial aims to help ameliorate, and possible swelling/inflammation in the area treated with SRS.

The MRI scans to be obtained at baseline (DTI +/- BOLD-fMRI) would be added on to the same scan performed for routine SRS planning for patients. Follow up MRI would be standard of care imaging and would be obtained regardless of whether the patient is on or off study. These scans do not involve any radiation exposure. There are no additional risks associated with the research scans (i.e., DTI and fMRI) aside from discomfort due to the additional 8-10 minutes of scan time required and/or mental fatigue experienced while completing the fMRI tasks. However, these scans are frequently performed as part of standard of care during presurgical planning without adverse effects. Some patients may experience claustrophobia in the MR scanner and may require the use of medications for this, as is prescribed routinely for brain MRIs when indicated.

***Risks of MRI Scans:*** There are no known effects from exposure to magnetic fields (MRI). In some cases, a special dye called a contrast agent may be given by injection to enhance the images. Subjects may experience an allergic reaction to the contrast. Most reactions are mild and result in a rash or itchiness. However, some people undergoing this procedure become anxious. The MRI uses powerful magnets, so if subjects have metal clips or plates in their body or a pacemaker, they should tell your doctor about it. All patients presenting for MRIs will be screened with questions by imaging staff for metallic implants prior to scheduling scans. MRI may not be appropriate if subjects have any metal (metal artificial joint) or electronic devices (like a pacemaker) in their body. The imager makes a loud, banging noise while it is taking

pictures. Subjects will be given a set of ear plugs to help with the noise. Subjects may experience feelings of claustrophobia or anxiety. Subjects may also experience some discomfort and tiredness from lying still in a confined space during the imaging. The treating physician will discuss any concerns about MRI scans with all subjects prior to enrollment on the study.

The directed neurocognitive evaluations are not standard of care unless a patient requires clinical referral to neuropsychology. Neuropsychological testing as described above is done verbally one-on-one with a licensed neuropsychologist. This is a 30-45 minute testing session that is frequently employed in clinical trials. One possible risk to neurocognitive testing is a possible increase in psychological strain in susceptible individuals (e.g., to the extent that thinking about their cognitive difficulties is stressful, patients might experience stress in being evaluated). However, these neurocognitive evaluations are designed to be non-stressful and to be used for patients who may have cognitive difficulties. Patients will be counseled that the testing is merely to assess particular functioning (short term memory, attention, etc) and that this would not affect their clinical care. These tests are not anticipated to be particularly stressful in any way and patients can stop the testing at any time. Patients may find it stressful to know whether they have deficiencies in their neurocognitive functioning. They can request to discuss this with the PI or neuropsychologist if they wish.

***Risk of Questionnaires:*** A questionnaire may contain questions that are sensitive in nature, or otherwise cause you emotional distress. Completing questionnaires can be tedious or boring. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns about your mental or emotional health after completing a questionnaire, you should talk to your study team.

As mentioned, all imaging and neuropsychological data will be kept in a file that will not contain patient-identifying information. Thus, the risk for a breach of confidentiality is minimal. Moreover, the data will be stored in password-protected files only on the computers of investigators directly involved in the research.

***Risks of Loss of Confidentiality:*** There is a potential risk of loss of confidentiality which will be minimized as outlined in the Privacy and Confidentiality section.

***Radiation Exposure from Imaging:*** As is the standard of care for radiation planning for brain radiotherapy, each patient will undergo one CT simulation of the head with a radiation exposure of 2.5mSv. This CT simulation is standard of care for patients on trial or off trial for planning brain radiation therapy. The principal investigator for this research study has determined and verified that all of the radiation therapy prescribed for this study would typically be performed as part of the standard medical care required to adequately treat the subject's condition.

## 15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Performing the neurocognitive testing could be stressful for patients. To minimize this risk, patients will be informed that their participation is completely voluntary and will not be required to proceed with answering questions if they feel that the process is stressful. Subjects may also decline to answer any individual question that makes them too uncomfortable. If a subject withdraws consent during the study, their entire encoded data file will be deleted from the research database and they will continue to receive routine clinical care. In addition, Dr. McDonald or a member of her trained staff will monitor the patient for any emotional distress and remind the patient that he/she may discontinue testing at any time if they do not wish to continue. However, Dr. McDonald has been performing this type of research evaluation with patients for over 15 years and less than 5% of patients experience an adverse reaction to the testing.

During initial trial enrollment, patients will provide informed consent to have their de-identified MRI and clinical data used in proposed project. During the DTI/fMRI scans, patient comfort will be monitored by the technician, who will check in with the participant after each scan to ensure optimal comfort. In addition, the participant will be provided with a hand help device that allows them to communicate with the MRI technician and signal the technician to stop the scan if they are to feel uncomfortable and need assistance. After the MRI data are acquired, the data are transferred via a secure network connection to a secured computer at the UCSD CMIG for off-line analysis. These data are retained in a locked office at the CMIG that is only accessible to Drs. McDonald and Hattangadi-Gluth, both of whom hold Associate Staff Medical privileges at UCSD.

## 16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Confidentiality of a subject's protected health information will be maintained by the following methods: study-specific records containing protected health information, and copies of study-related medical records, will be kept in locked filing cabinets at the Moores UCSD Cancer Center research administrative offices.

Computers containing access to protected health information will have password-access; and screen-savers will be utilized to prevent unauthorized viewers from inadvertently seeing information. Protected health information will be stored on secure servers. The servers supporting these studies are located inside a locked rack within the San Diego Supercomputer data center. The facility features restricted access by means of personal codes (PINs) and biometrics, and is monitored 24 hours a day 7 days a week. The electrical power is backed up by battery-powered uninterruptible power supplies, as well as by on-site generators. Both servers are behind firewalls configured to allow access only to credentialed personnel within the UCSD network. The servers run only those services necessary for current operations. Services not needed for current operations have been disabled. Velos, the clinical trials management system, maintains an additional internal access control mechanism via user names and passwords. Data transactions executed over our intranet are encrypted via Secure Sockets Layer.

Access to a subject's protected health information will be limited to those study personnel who need to use it to accomplish the purpose of the research, and the minimum necessary information to accomplish the purpose of the research will be collected, stored, used, and reported. When protected health information is sent outside the University of California, San Diego, it will be disclosed only to those parties listed in the subject's authorization, and an audit trail log will be maintained of what information was sent and to whom it was sent.

As introduced in section 9, patients will be assigned a random study identification number for purposes of organizing the data and the data for the study will be kept in 2 main files: the "central" file and the "code" file. After the data is collected, it will be stored in the "central" file (that will contain no patient-identifying information such as name, date of birth, MRN, etc.). A separate, password-protected "code" file will contain the mappings of patient name with their random study identification number. This file will be password-protected, with the password known only to CITI-trained study personnel, and it will be stored exclusively on the computer of the principal investigator. These patient identifiers will be destroyed following the collection and aggregation of the dataset, and thus the patient data will be officially de-identified at this time.
Subject identifiers will be destroyed by the PI at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is required by law.

## 17. POTENTIAL BENEFITS

Participation in this trial may benefit future subjects by advancing generalizable knowledge of treatments for subjects with cancer.

## 18. RISK/BENEFIT RATIO

The potential benefit is judged to outweigh risk; therefore, the risk/benefit ratio is in favor of benefit.

**19. EXPENSE TO SUBJECT**

All procedures not considered standard of care (including BOLD-fMRI, additional study sequences when necessary, and neurocognitive evaluation) will be paid for by the study.
The subject and/or their third-party insurance payor will be billed only for standard of care costs (including routine clinic visits, routine laboratory tests, routine imaging) and not for research-related procedures, associated with this study.

**20. COMPENSATION FOR PARTICIPATION**

There will be no payment to the subject for their participation in this study.

**21. PRIVILEGES/CERTIFICATIONS/LICENSES & RESEARCH TEAM RESPONSIBILITIES**

Dr. Hattangadi-Gluth, the principal investigator of this study, is a licensed physician in the State of California, with privileges at the University of California, San Diego Medical Centers. She will be responsible for the overall conduct of the study, recruitment, determining subject eligibility, and clinical evaluations.

Please refer to the Biomedical Facesheet for a list of the sub-investigators on this study.

All of the sub-investigators are licensed practitioners in the State of California with privileges at the University of California, San Diego Medical Centers. Their roles in the study will include recruitment of subjects, determining subject eligibility, and clinical evaluations.

Dr. Carrie McDonald, PhD is a board-certified neuropsychologist at UC San Diego with expertise in neuropsychology and neuropsychological testing and interpretation. Doctoral Students in Clinical Psychology (neuropsychology specialization) will help perform the Neurocognitive Testing under Dr. McDonald's direct supervision. Dr. McDonald is responsible for the oversight of the staff and delegated duties. She and Dr. Hattangadi-Gluth are also members of the Center for Multimodal Imaging and Genetics at UC San Diego that performs novel translational imaging projects.

Armin Schwartzman, PhD, biostatistician in the Center for Translational Imaging and Precision Medicine, will assist with the data analyses and statistical support.

The Moores UCSD Cancer Center Clinical Trials Office study coordinator will be responsible for the recruitment and consenting of subjects, as well as reporting adverse events to the study sponsor, and to the UCSD HRPP office. The study coordinator will also be responsible for completing the Case Report Forms (CRFs) and data clarification forms (DCFs), maintaining source documents, and serving as the liaison with the study sponsor.

The Moores UCSD Cancer Center Clinical Trials Office regulatory associate will be responsible for completing the IRB and ancillary applications, corresponding with the various committees, trial master file management, and serving as the liaison with the study sponsor.

Dr. Hattangadi-Gluth and all the sub-investigators on this study have completed the appropriate CITI training and their certificates are on file on the UCSD Cancer Center Clinical Trials Office shared network drive.

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**23. FUNDING SUPPORT FOR THIS STUDY**
This is an investigator-initiated protocol funded by a pilot grant from CTRI and an R01 grant from the National Institutes of Health.

**24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT**
Not applicable.

**25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER**
Not applicable.

**26. IMPACT ON STAFF**
The proposed study may involve the participation of nurses who work directly with Radiation Oncologists at UCSD. However, these individuals would not be expected to acquire novel skills or be expected to perform any duties that are outside of the normal duties of their profession. There is a funded study coordinator available for this study. There will be no excess nursing burden.

**27. CONFLICT OF INTEREST (COI)**
There is no conflict of interest, and the appropriate forms (i.e. 700U) have been submitted to the Conflict of Interest Office, via the Office of Contracts and Grants Administration (OCGA).

**28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES**
This study has been approved by the Moores UCSD Cancer Center Protocol Review and Monitoring Committee (PRMC) for review.

## 29. OTHER APPROVAL/REGULATED MATERIALS

This study has been approved by the UCSD Human Exposure Review Committee (HERC) for review.

## 30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable