Radiosurgery or Open Surgery for Epilepsy

Radiosurgery vs. Lobectomy for Temporal Lobe Epilepsy:

A Phase III Clinical Trial

Radiosurgery or Open Surgery for Epilepsy

Protocol
&
Manual of Operations

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Inclusive of DSMB amendments/updates through 9/13/2011

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1 SPECIFIC AIMS

The purpose of this study is to compare the effectiveness of Gamma Knife radiosurgery with temporal lobectomy in the treatment of patients with pharmaco-resistant mesial temporal lobe epilepsy. Based on the successful completion of a Pilot Clinical Trial showing that seizure-free rates were in excess of 80% and that toxicity was acceptable, there is equipoise for treating well-selected patients with either radiosurgery or temporal resection.

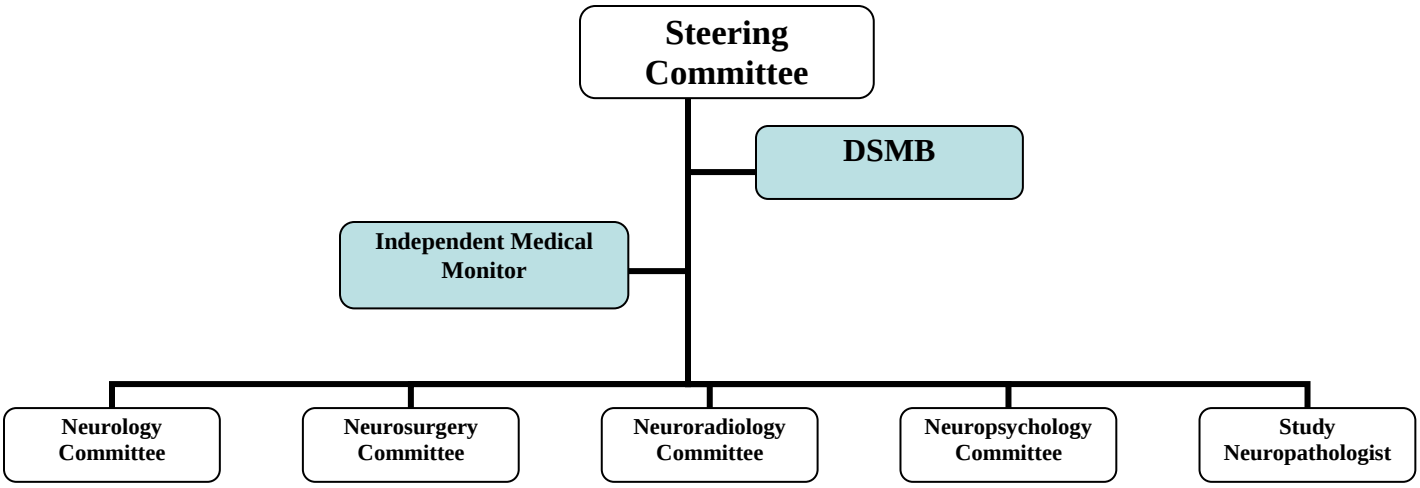
Aim 1: To compare the seizure-free outcomes and morbidity of Gamma Knife radiosurgery (GK) for patients with pharmaco-resistant temporal lobe epilepsy with those of open temporal lobectomy. Our primary hypothesis is that radiosurgery will be non-inferior to lobectomy with respect to seizure-free rates at 25-36 months following therapy (one-year of seizure freedom beginning 2 years after treatment). GK will be considered non-inferior to open temporal lobectomy if the one-sided 95% lower confidence bound for the difference in seizure-free rate between open temporal lobectomy and GK is less than 15%.

Aim 2: To compare the neuropsychological outcomes in patients undergoing radiosurgery and temporal lobe surgery, in particular with respect to verbal memory function for language-dominant hemisphere treated patients. Our hypothesis is that patients treated for speech-dominant temporal lobe seizures with temporal lobectomy will show greater reduction in verbal memory than patients treated with radiosurgery.

Aim 3: To determine what changes occur in the quality of life of patients with temporal lobe epilepsy following radiosurgical treatment as compared with open surgery. Our primary hypothesis is that there will be improvements (comparing baseline with 3 years post-treatment) in quality of life measures in both groups. Our secondary hypothesis is that both open surgery and radiosurgery subjects will undergo transient reductions in quality of life measures caused by treatment effects during the first year following treatment, but that quality of life will improve for subjects who become seizure-free, independent of treatment group.

Aim 4*:* To compare the cost-effectiveness of radiosurgery compared with open surgery. We hypothesize that radiosurgery will be cost-effective compared to temporal lobectomy over the lifetime of the patient*.*

2 ORGANIZATION OF THE PHASE III CLINICAL TRIAL



The Steering Committee will be chaired by the Principal Investigator (Barbaro), and will include Co-principal Investigator (Quigg), Study Radiation Oncologist (Sneed), Study Data Management Coordinator (Ward), Study Statistician (Lamborn), Study Radiation Physicist (Ma), Study Neuropsychologist (Broshek), Study Neuro-radiologist (Dillon), Study Neurologist (Laxer), the Chair of the Neurosurgery Committee (McDermott) and the Treatment Center Principal Investigators. Dr. Langfitt will function as the Study Health Economist, based on his experience studying the cost of chronic epilepsy and ATL. This group will have monthly conference calls to discuss the overall management of the trial, including contract issues, IRB approvals, recruitment issues, data collection and clinical follow-up (including adverse events). They will not have access to outcome summary data in order to maintain blinding for the overall results of the trial.

The Neurology Committee will be chaired by the Co-PI (Quigg) and will include Study Neurologist (Laxer) and the Neurologists from all of the Treatment Centers. Dr. Laxer and Dr. Quigg will provide review of entrance criteria. The entrance neurology data (neurological examination summary, EEG and video-telemetry reports) will be reviewed within 5 business days of arrival at the Study Center. In addition, the Neurology Committee will review the neurology evaluations including seizure diaries, medications, including changes in medications during the trial, visual field reports, and EEG data. This Committee will meet twice yearly: once at the American Epilepsy Society and once at a national neurology meeting of their choice. The chair of this committee will report to the Steering Committee as needed. As the Study Neurologist is not a treating physician, he will provide outside, independent review of all neurologic aspects of the trial, including entrance criteria and neurological AEs. These data will be included in each DSMB report. Dr. Laxer will also serve as the central “event adjudicator”. He will review the seizure classification of all subjects entered into the trial and will review any seizure diary changed by the blinded neurologists as they review seizure diaries.

The Neurosurgery Committee will be chaired by the Dr. Michael McDermott as an independent investigator. As he will not directly participate in the treatment of any patients, he can provide relatively unbiased advice to the neurosurgeons on this committee. Dr. McDermott was an advisory participant in the Pilot Trial and is Co-director of the Radiosurgery Program at UCSF. The Neurosurgery Committee will consist of all neurosurgeons participating in this trial and will meet semiannually at the Congress of Neurological Surgeons and American Association of Neurological Surgeons. A subcommittee of the Neurosurgery Committee will consist of Dr. McDermott and three neurosurgeons from Treatment Centers who will review the three-month post-operative MRIs for subjects who have undergone temporal lobectomy. A determination of whether there has been adequate resection of temporal lobe tissue will be made. Any subject who is determined to have an inadequate resection will be considered a “protocol

violation". (See data management and statistical sections). The Chair will report to the Steering Committee following each Neurosurgery Committee meeting and will provide data for the DSMB reports.

The Neuroradiology Committee will consist of the three neuroradiologists from UCSF who will be reviewing the entrance and follow-up MRIs for the entire study. They will be available to review studies within 48 hours of receipt by the Study Center to determine eligibility requirements. They will review all subsequent MRIs for presence of new abnormalities (adverse event documentation) and presence or absence of radiation-related edema. The results of these reviews will be sent back to the Treatment Centers, although it will be expected that each Treatment Center will have reviewed results of their individual subjects' studies prior to sending them to the Study Center. As the Neuroradiology Committee will all be present at the same institution, they will determine the need for meetings on an ad hoc basis. The Chair of this Committee will report back to the Steering Committee as needed. Their reports will be part of each DSMB report

The Neuropsychology Committee will consist of the Study Neuropsychologist (Broshek) and the neuropsychologists from each Treatment Center. This group will meet yearly at the American Epilepsy Society Annual Meeting to review the conduct of the trial with respect to the neuropsychological data collection and to ensure adherence to standard administration procedures. The purpose of these meetings is to be sure that all Treatment Centers are continuing to work within the protocol and to discuss any possible issues with respect to neuropsychological outcome measures. They will not have summary data that indicates treatment group; these data will be made available to the Independent Medical Monitor and to the DSMB. Toxicity data will form a portion of each DSMB report. The Chair of this Committee will report back to the Steering Committee as needed.

It was determined that there is no need for a separate radiation oncology committee or radiation physics committee at the start of the trial. The Steering Committee can create such committees if issues develop that require review by these groups.

In addition, the Study Center will consist of individuals whose role will be statistical support and analysis, data collection and review, coordination of the protocol with Treatment Centers and production of reports for the Steering Committee, the Data and Safety Monitoring Board and eventual publication of trial results. We have designated Dr. Lamborn who has been a keystone member of the research team as the "blinded" statistician. As such, she will continue as a member of the steering committee and provide input on statistical issues related to study conduct without knowledge of patient treatment information. Dr. Yan, will serve as our "unblinded" statistician. She will be responsible for providing data for presentation to the DSMB and will have complete access to patient data while the study is ongoing. They will work with Mariann Ward, MS, NP who will function as the Study and Data Management Coordinator. Ms. Ward performed similar functions in the Pilot Trial by communicating with Treatment Center Coordinators throughout the study. Nearly 100% data collection was achieved for the Pilot Trial.

The Data Management Coordinator will act as the primary contact person for data management issues. Working in conjunction with our Data Management Group, VisionTree, she will be responsible for clinical case report form design, its implementation in the database system and its' maintenance. Our Research Center Administrative Analyst will assist in production of reports for the monthly Steering Committee conference calls and the DSMB reports. She will also manage ongoing administrative organization such as updating investigator, site coordinator, and site clinic personnel contact information.

The Study Neuropathologist (Tihan) will work independently to review all tissue slides obtained from patients who have temporal lobectomies and on the occasional subject who may require surgery following radiosurgery. This would include subjects who require surgery for significant brain edema (1 subject out of 30 in the Pilot Trial) or those who request temporal lobectomy during or after the three-year follow-up period. The Study Neuropathologist will report directly to the Steering Committee. The neuropathology review of tissue samples will allow an assessment of the degree of homogeneity of the medial temporal lobe structures removed in temporal lobectomy cases. While little or no tissue will be obtained from subjects randomized to the radiosurgery arm, it is assumed that a similar distribution of diagnoses will exist for both arms of the study due to randomization. There is a good correlation between MRI findings of

mesial temporal sclerosis and histo-pathological findings. However, the presence of other abnormalities may influence outcome. The ability to evaluate a consecutive series of 117 samples in this protocol will provide important information to corroborate those findings. Significant heterogeneity of the samples could be one explanation for lack of seizure freedom in these cases.

The Independent Medical Monitor (IMM) will be a neurologist, (Dr. Andy Cole). This individual will not be directly involved with patient recruitment, treatment or patient follow-up evaluations. The IMM will be provided with unblinded data in order to monitor adverse events and outcomes. Specifically, the IMM will monitor seizure-related and other medical adverse events; will review all AE reports related to treatment and the post-treatment neuropsychological testing. This individual will be available to participate in monthly Steering Committee conference calls to inform the Committee if there are new AEs that might influence the conduct of the trial. The IMM will supply confidential reports to the DSMB at regular intervals. In addition, should any death or serious AE occur, the IMM will generate an urgent report to the DSMB Chair within 48 hours. The IMM will review stopping guidelines on a regular basis with the DSMB making the ultimate decisions on suspension of enrollment or other changes.

3. GENERAL STUDY DESIGN

Introduction

The ROSE Trial is a multicenter, prospective, randomized trial of Gamma Knife radiosurgery (RS) versus anterior temporal lobectomy (ATL) for patients with unilateral mesial temporal lobe epilepsy (MTLE). This is an intent-to-treat trial. Since all randomized patients will be included in analysis, all reasonable efforts are required to minimize losses to follow-up.

The recruiting goal is randomization of 234 patients (117 each arm) in ~14 treatment sites in a three-year enrollment window.

Trial Design and Goals

Each patient will require "standard" presurgical evaluation and a diagnosis of unilateral MTLE. Eligibility requires a three month pre-enrollment/randomization seizure diary period. Each patient will be followed for 36 months (three years) postoperatively.

The ROSE Trial has 4 main goals.

1) To compare the seizure-free outcomes and morbidity of RS versus ATL. Our primary hypothesis is that radiosurgery will be non-inferior to lobectomy with respect to seizure-free rates at 25-36 months following therapy (one-year of seizure freedom beginning 2 years after treatment). The study is powered to allow a 15% difference between final seizure-remission rates to define "noninferiority".

2) To compare verbal memory in the subset of dominant hemisphere surgery patients

3) To compare quality of life by standardized QOL measurements as well as in evaluations of functional outcomes (driving, employment, etc).

4) To compare direct and indirect costs

Patients with MTLE, defined as electrophysiological (EEG) and *ipsilateral* radiographic (MRI) evidence of medically refractory epilepsy arising from one temporal lobe who would otherwise be offered open surgical resection of their epileptic focus, will be offered entry into this trial. Such patients will already have undergone extensive screening including neurological evaluation, trials of numerous antiepileptic medications, MRI, neuropsychological evaluation including Wada test, and video-telemetry.

Subjects will be randomized into two groups: RS or ATL. Randomization will be stratified according to treatment center and side (language dominant or language non-dominant). As Specific Aim 2 is to show that RS is less likely to result in significant reductions in verbal memory, it is important that there be a comparable number of dominant patients in the two treatment groups. Because all patients will have failed optimal medical management, there will not be a "best medical management" group. Patients will be treated within two months of randomization. This aspect is important in keeping the overall length of the study within a six-year period and as an incentive for patients to enter the study. As many epilepsy surgery centers have longer waiting periods for surgical treatment, the ability to move quickly to treatment should act as an incentive to enter the trial. In addition, one reason that eligible patients gave for not entering the Pilot Trial was the long delay in response for radiosurgery. Entrance in this protocol will offer eligible subjects rapid advancement to treatment.

Evaluation for inclusion into the trial

As part of the preoperative screening visit, each candidate subject will be assigned a study number based on the Treatment Center code and the sequential number of patients screened at that site. Not only will this identification system provide proper anonymity, it will allow tracking of the proportion of patients who successfully proceed to enrollment and consent. Other than the MRI, the Study Monitoring Center will not attempt to verify independently the accuracy of the clinical data provided, with the caveat that review of primary data will be at the prerogative of the Neurology Committee.

All patients will be evaluated as is typical for patients being offered temporal lobe resective surgery. The minimum testing for each patient will include the following:

1. Complete medical and neurological history, physical examination including complete neurological examination and complete listing of all medications (special attention to anti-epileptic medications).
2. Completion of three-month (12 week) seizure diary with documentation of at least three complex partial seizures accrued during the diary period. At least 1 complex partial seizure must have occurred within the last 8 weeks of the diary (while receiving adequate antieleptic drug therapy).

Seizure diaries can consist of any three month (12 week) sample that is:
-Sequential
-Reflects stable anticonvulsant type/use (ie. No discontinued or started anticonvulsants during diary)
-Site may exclude one month interrupting diary (noncontiguous) for imposed anticonvulsant abnormalities (seizure cluster due to sickness, medication interruption during monitoring unit admission, or other extenuating circumstances). The balance of the remaining seizure diary after exclusion must total 12 weeks.
-Seizure diaries may be obtained at any point during the pre-surgical, pre-enrollment period, including after in-patient monitoring unit admission but before enrollment
-Since seizure diaries are inclusion criteria, diaries of insufficient duration must be continued to meet enrollment criteria before official enrollment.

3. Formal visual field examination (Humphrey 120 point exam).
4. Standard scalp EEG.
5. Videotelemetry with EEG with the use of scalp and/or invasive recordings (subdural or depth electrodes) sufficient to diagnose a unilateral mesial temporal lobe seizure focus.
6. High resolution MRI (1.5T minimum) with evidence of mesial temporal sclerosis (hippocampal atrophy and/or increased T-2 hippocampal signal) on same side as EEG focus. The study should be performed within 18 months of enrollment. Refer to Radiology Protocol for recommended sequences. (Page 21)
7. Wada test including assessment of memory function for each temporal lobe and assessment of language lateralization (See Appendix for Wada protocol guidelines). All centers will report the degree of language dominance divided into a 5 point scale: 1=left only, 2=left>right, 3=symmetric, 4=right>left, 5=right only. Even without standardized reporting methods, there were no ambiguities in Wada test interpretation in labeling patients by language dominance in the Pilot Trial. The language dominant hemisphere will be defined as the hemisphere with exclusive or predominant language function. Subjects with a number of 1 or 2 will be considered left dominant, those with a 4 or 5 will be considered right dominant. Those with 3 (symmetric) will be considered not to have a language dominant hemisphere for the purpose of verbal memory analysis.
8. The minimum battery for neuropsychological testing is listed in Table 1. We specify that the initial battery must be acquired during the pre-enrollment period with an ongoing stable anticonvulsant regimen.

Table 1: Inclusion neuropsychological and quality of life battery

Intelligence	-Wechsler Abbreviated Scale of Intelligence (WASI)
Language	-Boston Naming Test (1983) - 60-item version -Auditory Responsive Naming Test (Hamberger et al)
Verbal Memory	-California Verbal Learning Test - Logical Memory I & II subtest from the Wechsler Memory Scale-Third Edition
Visual Memory	-Rey Complex Figure Test -Brief Visual Memory Test
Cognitive Processing Speed	-Trail Making Test, Parts A & B
Mood	-Beck Depression Inventory-II -Beck Anxiety Inventory
Quality of Life	-Quality of Life in Epilepsy (QOLIE-89)

Entry and exclusionary criteria

Adults (18 years and older) of either gender who would otherwise be eligible for temporal lobe resection will be offered enrollment for randomization to RS or ATL.

1. Seizure type: Patients must have simple and/or complex partial seizures with or without secondary generalization.
2. Seizure Frequency: Patients must have at least three complex partial seizures during the three month (12 week) baseline seizure diary period with at least 1 of 3 seizures occurring within the last 2 months (8 weeks) while receiving adequate antiepileptic drug therapy.
3. Patients with electrographic evidence of seizures arising from one temporal lobe, with radiographic evidence (hippocampal atrophy or increased T-2 signal) of mesial temporal sclerosis

in the same temporal lobe will be included. Patients with normal MRIs, bilateral hippocampal damage, or clear "dual pathology" of a cortical lesion will be excluded.

4. Subjects should be on stable doses of antiepileptic medications for at least three months prior to treatment.
5. All female patients of childbearing age will have documented that they are using a safe and effective means of birth control and will have a negative urine or serum pregnancy test completed within 1 week prior to their treatment (irrespective of treatment arm).
6. Patients should be able to understand the potential benefits and risks of surgical therapy to the extent required for epilepsy surgery to proceed clinically. For these reasons, only patients 18 years and older will be accepted. Acceptability for enrollment varies with general IQ.
    a. If IQ ≥ 70 then the patient is accepted.
    b. If IQ < 70 centers can offer the option to conduct a formal evaluation as an alternative method of assessing capacity to consent to participate. The evaluation should follow local IRB protocols at each site. It should be conducted by a physician or psychologist with expertise in capacity evaluation who is not involved as a center investigator in the ROSE Trial. Examples of formal competency assessment that are suggested, but not required for use in the capacity evaluation include the MacArthur Competence Assessment Tool – Clinical Research (MacCAT-CR) and the Assessment of Consent Capacity—Randomized Clinical Trials (ACC-RCT)See Appendix 2 for summary of determination of competency for consent.
7. Patients with any focal neurologic deficit that would make it difficult to detect a new radiation-associated injury will be excluded. All patients will receive formal visual field testing *(Humphrey 120 point exam)* prior to entry into the protocol. Patients with visual field deficits will not be offered entry into the protocol, but will likely be eligible for standard treatment (open surgery).
8. Patients with radiographic evidence of other pathologies such as vascular malformations or tumors will be excluded from this study.
9. Patients with diabetes mellitus will be excluded from this study because radiation injury to the brain is more common in patients with this condition.
10. Subjects should not have significant psychiatric conditions that would make accurate assessment of seizure frequency difficult, as judged by the principal investigator. Such conditions include a history of non-epileptic seizures, psychosis (other than post-ictal psychosis) and severe mood disorders including suicide attempt within past 12 months or noncompliance with psychotropic medications.
11. Patients with a history of significant past or present medical disorders determined severe enough to prevent participation in a surgical trial by the principal investigator (e.g. renal, hepatic, cardiovascular, rheumatic fever, gastrointestinal or hematological abnormalities, or cancer with a metastatic potential) are excluded.
12. Patients with any progressive neurological disorder (such as multiple sclerosis or systemic lupus erythematosis) are excluded.
13. Patients with a history of poor compliance with past antiepileptic drug therapy as judged by the principal investigator are excluded.
14. Patients with a recent history of abusing drugs or alcohol with significance as judged by the principal investigator are excluded.
15. Patients who are receiving any investigational drugs at the time of enrollment are excluded.
16. Patients with current use of vigabatrin are excluded. Past use does not exclude a patient pending a normal formal visual field test.
17. Patients who can not be anticipated to participate for the full 36 months of the trial will be excluded.
18. Native English speakers from the U.S. or other English speaking countries or patients who learned English before age 5 and were educated in English. Spanish speaking patients can be included as long as the study site can provide an officially translated (IRB approved) consent form in Spanish. Non-Spanish speaking patients with English as a second language (ESL) and/or non-English and non-Spanish speaking patients can be included only under the following conditions: 1) the study site must be able to have the consent form translated into the patient's native language using an official translator, and 2) the study site's neuropsychologist must be willing and able to assess the patient at baseline and post-treatment at 12, 24, and 36 months in that patient's native language to ensure the patient's safety.

Discussion of inclusion and exclusion criteria

This study will attempt to demonstrate that GK is an effective alternative to ATL in treating patients with MTLE. The inclusion criteria are designed to recruit a homogeneous sample with unilateral MTLE defined by MRI and concordant video-EEG localization of seizures. In the Pilot Trial, these criteria led to three-year rates of seizure remission similar to those seen in prospective trials of standard ATL.

Although we require interictal EEG as a pre-surgical evaluation, the specificity and positive predictive value of interictal epileptiform discharges (IED) would not improve homogeneity of the sample and may unnecessarily exclude patients from eligibility. Of our 30 patients in the Pilot Trial, only 60% had IED on routine, preoperative EEG. No subjects had IED contralateral to GK. One subject had "ipsilateral > contralateral sharp transients" of unclear clinical significance. Remission of seizures after GK bore no relationship to presence or absence of IED.

The experience with ATL at the University of Virginia surgical program agrees with that of the Pilot Trial. Out of 136 cases of histopathologically-confirmed HS after ATL performed between 1991-1999, presence or concordance of IED did not affect the rate of Engel class 1a-b seizure remission (remission = 74%) (Mark Quigg and Nathan Fountain, University of Virginia, personal communication). Similarly, in the experience of the multicenter prospective evaluation of epilepsy surgery, as well as in retrospective studies of "homogenous" MTLE, IED in their presence or concordance did not predict seizure remission. Unilateral HS on MRI, on the other hand, is a strong predictor or correlate of remission.

We acknowledge, however, that the prognostic value of IED remains controversial. Radhakrishnan et al found that preoperative IED correlates with outcome. Likewise, Gilliam et al found that concordant HS and IED confined to ipsilateral scalp correlates with remission, and that surgical outcome is worse in patients with concordant MRI and ictal EEG findings but with non-lateralizing IED.

Notwithstanding the controversy over the prognostic value of preoperative IED, the trial is designed to enroll patients for whom investigators deem ATL an appropriate procedure. Accordingly, we allow the inclusion of patients who required intracranial recordings as long as ictal intracranial EEG is concordant with clearly unilateral HS on MRI. In the University of Virginia experience, 70% of patients with lateralizing seizures on intracranial video-EEG who undergo ATL achieve seizure remission. Thus, use of intracranial electrodes does not preclude good surgical outcome. The presence of even 1 seizure on the side contralateral to MRI changes will exclude potential subjects from this trial.

Given that different physicians apply different criteria for which patients may qualify for ATL, the design of our randomized trial will allow differences in referral patterns to distribute evenly between the two treatment arms. Therefore, we feel the current criteria maximize possible recruitment into the protocol while allowing for small differences in physician preference, adhere to the standards of care of presurgical localization, and assure that only patients who would normally obtain an ATL - those with unilateral MTLE be considered for inclusion. To facilitate effects of operative procedures on seizure outcome and to not confound neurocognitive or mood outcomes, anticonvulsant medication regimens should remain stable throughout the course of the trial. Vagal nerve stimulation (VNS) is considered an anticonvulsant for the purposes of the trial and must be set to stable therapy or inactivity as present during the baseline,pretreatment period. Indwelling VNS electrodes are permitted in agreement with each center's policies on brain MRI imaging since required neuroimaging for inclusion and followup must still be obtained.

It is expected that patients of both genders, with a broad mixture of minority groups and over a relatively wide spectrum of ages will be included. This is typically the case in active epilepsy surgery centers. Patients younger than 18 have been excluded because there is evidence from the oncology literature that young patients are more susceptible to radiation injury although this primarily applies to very young children receiving whole-brain radiation. In addition, as the oncogenic potential from radiation is based on the length of time from radiation exposure, extremely young patients are excluded. Finally, there is evidence that very young patients with MTLE have worse seizure-free outcomes from standard temporal resections. No upper age limit has been set because the general population of patients seen for this disorder rarely includes patients over 60. There is no obvious reason to exclude elderly patients unless they have a co-morbid condition (diabetes mellitus) that would increase their risk of radiation injury. In fact, radiosurgery could be an excellent alternative to ATL in older patients.

The option to enroll a candidate with IQ<70 through local means of capacity determination is included to allow participation by subjects who have capacity to consent, but do not meet the IQ cutoff specified in the protocol. IQ >= 70 is a common proxy for capacity in clinical trials, but IQ measures are subject to

error (due to multiple variables, including medications, seizure disorder, and day to day fluctuations in energy and alertness). Also, many patients with IQ < 70 demonstrate understanding of information regarding participation in clinical trials at a level similar to intellectually normal patients. This option reflects the standard of clinical practice in that these patients would normally be asked to consent for standard epilepsy surgery.

In order to fully assess the potential safety of GK in otherwise normal brains, patients with pre-existing neurological deficits that might mask radiation injury will also be excluded. Patients with pre-existing visual field defects will be excluded because visual field defects can arise from injury to the lateral temporal lobe (typically medial superior quadrantanopsia). Only one patient was excluded from entry into the Pilot Trial based on this criterion. In addition, ongoing treatments that may induce visual field defects (current vigabatrin use) will trigger exclusion.

Because there is a well-established alternative to GK, patients should be able to understand potential risks and sign their own consent forms. For this reason, patients with severely low IQs or severe psychiatric conditions are to be excluded. Patients are expected to have more than three seizures per month when averaged over three months. This lower limit was placed to be sure that adequate statistical comparisons can be made between pre-treatment and post-treatment seizure frequency. Should this form of treatment prove effective in this homogeneous population, future protocols can have wider acceptance criteria. The exclusion of patients with a history of poor compliance with other protocols, or with a history of drug and alcohol abuse is intended to ensure that all patients entered into the protocol have a high likelihood of completing the study, and that there are no reasons for ongoing seizures (i.e. alcohol or drug related) other than treatment failure.

Clinical Trial: Patient Activity Flowsheet

The following is a suggested patient-by-patient flow sheet from new referral to final visit. The trial has been designed to maximize recruitment by "embedding" standard patient-assessment tools and protocols into the usual practices of tertiary epilepsy centers.

Pre-evaluation/pre-EMU admission

Group: all potential epilepsy surgery candidates
Task:
- ROSE Trial pamphlet
- Consider seizure diary

EMU admission

Group: Probable MTLE/ATL candidates
Task:
- Consider seizure diary to start post admission

Epilepsy Surgery Discussion/Meeting

Group: Probable MTLE/ATL candidates
Task:
- Fill out ROSE Trial Pre-Treatment Screening Data Forms screening worksheets on <u>all</u> temporal lobe epilepsy surgery candidates at your center.

Initial post-admission visit (note: some study sites may combine this with Study Screening Visit below)

Group: Probable MTLE/ATL candidates
Task:
- Review trial with patient
- Study Screening Clinic Visit/Consent

Group: Definite ROSE Trial candidates
Task:
- Sign consent
- Treatment Site PI-> obtain consent, verify seizure diary, perform neuropsychiatric structured interview CRF

- Study coordinator-> send MRI to UCSF Study Center and transmit all other subject Inclusion/Exclusion screening data to Study Center via upload for Study Center verification of baseline data and determination of study eligibility.
- Following Study Center review of subject eligibility, the individual site study coordinator will be notified of patient's official acceptance into the study. For those patients who are accepted for study enrollment, the study coordinator will then receive notification from the Data Management Center directly, regarding the randomly assigned treatment arm assignment.

Randomization

Group: Consented, eligible patient

Task:

- Study Coordinator->Receives randomized treatment arm assignment from the Study Data Management Center. Coordinator verifies site blinded and unblinded personnel for that subject
- Assign blinded and unblinded neurologist
- Scheduling for ATL/RS
- Instruct patient on "Blinding Techniques"

Treatment/PO M00

Group: Randomized ATL/RS patient

Task:

- RS group at treating center transmits radiosurgery treatment plan to UCSF for approval, prior to treating patient; otherwise standardized temporal lobectomy date is scheduled by study site. Post op follow-up care per protocol and study site.
- Entire study team must be notified of patient and the matched blinded staff so as to best maintain blinded status of blinded staff
- Pregnancy testing (urine or serum) within 1 week prior to treatment for female patients

PO M01 (Phone visit-see below)

Group: Treated patient

Task:

Study coordinator:

- Complete Telephone Follow-up Visit and CRF
- Schedule an outpatient visit if noncompliance, protocol confusion, or adverse event is reported or apparent

PO M00-03

Group: Treated patient

Task:

- Standard postoperative visits and evaluations for each treatment arm, as designated in protocol.

PO M03-36 (except for "phone visits" below)

Group: Treated patient

Task:

Blinded neurologist:

- Focused Neurological Exam CRF, Seizure and Healthcare Utilization diary review and classification and completion of Post-Treatment Seizure Classification and Frequency CRF, Headache and Mood CRF, Actual Life Changes in Epilepsy CRF, Hopkins Verbal Learning Test CRF (not required at 3 month visit).

Unblinded neurologist:

- Adverse Events CRF as needed, treatment decisions

Study coordinator:

- Collect any remaining data and CRFs as needed

- Verify completeness of CRFs
- Transmit data to UCSF Study Center
- Schedule upcoming additional visits/studies (neuroimaging, NPT as specified in protocol, treatment-oriented studies as determined by unblinded neurologist)

PO M01, 25, 26, 28, 29, 31, 32, 34, 35 (Phone Visits)

Group: Treated patient

Task:

Study coordinator:

- Complete Telephone Follow-up visit CRF
- Schedule an outpatient visit if noncompliance, protocol confusion, or adverse event is reported or apparent

Roles and Responsibilities of Clinical Trial Staff

Blinded and Unblinded Clinical Trial Staff Personnel: Roles and Responsibilities

After randomization, each trial site needs to insure that each patient's assignment to ATL or RS is blinded to all personnel except when specifically noted. In general, blinded staff supply data relevant to specific aims that requires subjective interpretation; unblinded staff are responsible for findings and clinical decisions based upon them.

Unblinded personnel

Study Coordinator - "point person" responsible for

- All data transfer and communications with study center
- Patient scheduling
- Data acquisition during patient's course through study which may include CRF verification or completion not specified below.

Unblinded Neurologist – physician responsible for

- Minimum requirement: board-eligible, board-certified neurologist; preferentially this will be the main study neurologist or treatment center PI.
- Adverse Events CRF
- Health and safety monitoring, treatment decisions

Unblinded neurosurgeon and radiosurgeon

- Treatment surgeons and allied staff are necessarily unblinded. If study sites are neurosurgically-based, each site must arrange visits to maintain staff blinding. Obviously, the treating neurosurgeon and radiosurgeon cannot participate as a "blinded neurologist" in the study.

Blinded personnel

Blinded Neurologist

- Minimum requirement: board-eligible neurologist (therefore, clinical neurophysiology/epilepsy fellows are eligible, but residents are not)
- Neurological Examination CRF
- Hopkins Verbal Learning Test CRF
- Seizure diary verification and completion of Post-Treatment Seizure Classification and Frequency CRF
- Headache and Mood CRF
- Actual Life Changes in Epilepsy CRF

Blinded Psychometrist/Neuropsychologist

- Since the initial neuropsychological evaluations will be performed as clinical evaluations prior to study enrollment, these evaluations will be unblinded as they are part of standard clinical care and will occur prior to randomization.
- Each post-enrollment neuropsychological evaluation conducted as part of the ROSE Trial protocol should be blinded. For sites that have a neuropsychologist and a psychometrist, both should be blind to the patient's treatment condition.
- Neuropsychological study personnel (neuropsychologist and psychometrist) should refrain from asking the patient any questions about treatment, seizure remission, or course of symptoms as this might result in disclosure of information pertinent to treatment condition, resulting in unblinding.
- In the rare event that a more extensive clinical neuropsychological assessment is required due to a patient's postoperative complications, the neuropsychologist may need to be unblinded in order to provide appropriate clinical care. In such rare situations, the study site should alert the study neuropsychologist (Broshek) or study neurologist (Quigg) prior to breaking the blinding. For those sites with a psychometrist, the psychometrist should still remain blind to the patient's treatment condition even in this circumstance.

Blinded Examination Specifications

- Each site must provide a large hat/s sufficient to cover the complete scalp for the purpose of obscuring post-surgical scalp and skull abnormalities. This hat must be worn during sessions with blinded personnel.

- In follow-up clinic visits, we recommend that the study coordinator issue the hat and remind patients about avoidance of disclosing information that could lead to inadvertent unblinding. In neuropsychological assessments, each treatment center will be responsible for developing the protocol to insure that patients are "hatted" and appropriately instructed before meeting with the neuropsychologist or technical staff.

Postoperative Clinical Visit Specifications

- The order by which patients will be evaluated during each postoperative visit will be

1) Study coordinator

- assignment of hat/blinding instructions
- pre-physician information
- data and CRF acquisition and completion, as needed, not otherwise specified below

2) Blinded neurologist

- obtain data and complete blinded CRFs as specified:
  1. Neurological Examination CRF
  2. Hopkins Verbal Learning Test CRF
  3. Seizure diary verification and completion of Post-Treatment Seizure Classification and Frequency CRF
  4. Headache and Mood CRF
  5. Actual Life Changes in Epilepsy CRF

3) Unblinded neurologist

- review of blinded CRFs
- completion of unblinded CRFs as needed, including Adverse Events CRF
- clinical decisions (if needed)

4) Study coordinator

- debriefing and scheduling

5) Blinded Neuropsychologists/Psychometrists

- visits to be to be scheduled per protocol at 12, 24 and 36 month post-op. Tests administered, as outlined in the protocol, and corresponding CRFs are to be administered and completed in a blinded manner.

Seizure Classification and Central Adjudication

In this trial, "seizure remission" (defined as the absence of complex partial seizures with or without auras) from months 24-36 serves as a primary outcome measure. To ensure that this condition is determined in a rigorously unbiased manner, we supplement the assessment of the blinded neurologist with central adjudication.

During the clinical interview with the blinded neurologist, changes to the patient's coding in either event type or counts will be flagged for later blinded review by a central seizure diary adjudicator. Although primary outcome will be determined by data provided by the local blinded neurologist, we will evaluate and report discrepancies in post hoc analysis. The processes of blinded review of seizure diaries and the role of the central adjudicator are detailed in Post Treatment Follow up.

4 RANDOMIZATION

Subjects will be randomized into two groups: RS or ATL. Randomization will be stratified according to treatment center and side (language dominant or language non-dominant).

Randomization and registration

As previously stated, all eligible subjects will be assigned a Study Number, based on the Treatment Center code and the sequential number of patients screened at that site, for the purpose of tracking potential subjects. Data will be transmitted to the Study Center including all of the pre-treatment evaluations. All patient identifying information will be removed from the records. All subsequent communication will include only subject numbers and initials. The Study Center will distribute this information to the relevant individuals for evaluation (Neurological history and examination, EEG and video telemetry to the Study Neurologist, radiological studies to the Study Radiologist). As the only data from the neuropsychological screen will be an IQ cutoff, this will be reviewed by the Study Neurologist. Once a center enters all entry data into the database, the clinical information will be accessed and reviewed by Dr. Quigg (primary neurologist) or by Dr. Laxer (if Dr. Quigg has indicated that he is not available) and radiological studies will be sent to the UCSF Neuroradiology team. These data will be reviewed within 5 working days. If clinical and radiological assessments indicate that this subject is appropriate for the study, the subject will be assigned to a treatment arm by the Data Management Center based on the randomization scheme. This information will be entered into the database and the Study Coordinator at the Treatment Center will be informed of the randomization assignment via e-mail. All subsequent communication regarding this subject will include the subject's Study Number and initials. The members of the Steering Committee will remain blinded to the treatment assignment.

5 RADIOSURGICAL TREATMENT

In the month prior to treating the first patient at each Treatment Center, a preliminary MRI will be transferred to the Treatment Center by the UCSF Study Center for practice planning. The practice plan will be transmitted back to the Study Center for review. Only after successful completion of this practice run will a Treatment Center be allowed to schedule an actual subject for treatment. In the Pilot Trial, this process proved to be extremely helpful in discovering various problems with electronic transfer (firewalls and other technical issues). In addition, it prepared the members of the Treatment Center for subsequent treatment of actual patients, thereby avoiding unnecessary delays.

Patients will be treated according to each Treatment Center's radiosurgical protocol. This will include placement of an intravenous line for administration of medications. Sedative medications such as Ativan will be encouraged (based on individual subject tolerability and other clinical issues) in order to reduce the chance of seizure occurrence during MRI or radiosurgical treatment. Pin sites will be prepared with skin antiseptic solution and injected with local anesthetic. The stereotaxic frame will be secured to the skull

with four pins. Patients will be taken to the MRI unit and receive a stereotaxic MRI. High resolution MRIs (1.5T minimum) will be obtained prior to radiosurgical treatment using the following protocol (partial details listed below, refer to the Radiology Protocols section in this Manual for complete MRI protocol).

Six sequences will be included in each examination including:

1. T1 sagittal localizer (TR=600; TE=MIN; FOV=30)
2. T2 coronal FLAIR images (TR=10,000; TE=140; FOV=22x16)
3. Coronal 3D SPGR images (TR=36; TE=MIN; FOV=26)
4. Axial with Gadolinium (TR=600; TE=MIN; FOV=30x22)
5. Coronal with Gadolinium (TR=600; TE=MIN; FOV=30x22)
6. Axial FSE (TR=3000; TE=90; FOV=26)

MRI data will be transferred to the Gamma Knife computer and treatment planning will be carried out in a manner that is routine for the Treatment Center. This typically involves consultation with the Treatment Center radiation oncologist and physicists.

After a treatment plan is developed, it will be transferred electronically to the Study Center for review. Each patient will receive radiation to the mesial temporal lobe during a single treatment session. The amygdala and anterior 2cm of the hippocampus as well as the immediately adjacent parahippocampal gyrus will be included in the radiosurgical target (treatment volume to range from 5.5-7.5cc). Patients will receive 24Gy to the 50% isodose line using an unlimited number of isocenters (likely to range from six to 30). The lifting of a restriction on the number of isocenters is the only change from the dose planning used in the Pilot Trial. Improvements in Gamma Knife technology (Automatic Positioning System, APS) have made it possible to deliver a more conformal radiation field using multiple isocenters distributed evenly over the treatment volume. All Treatment Centers have APS on their Gamma Knife units. In addition, the brainstem and optic nerve plus chiasm will be outlined. An assessment of maximal dose to these structures will be made and, if the tissue tolerance limits (10 Gy and 8 Gy, respectively) are exceeded, adjustments to the treatment plan will be made. Plugging patterns will be used to achieve as close to 100% coverage of the target volume as possible without exceeding safety limits. These parameters will be reviewed by members of the Study Center prior to actual treatment for each subject. This protocol is identical to that used in the Pilot Trial and resulted in no treatment violations.

Figure 1 shows a representative treatment plan from the Pilot Trial. Radiosurgical treatment will require approximately 60-90 minutes after the patient is placed into the treatment unit. During that time the patient's blood pressure, oxygen saturation, and neurological condition will be monitored. Typically, patients will receive a dose of Ativan or similar drug just prior to placement into the Gamma Knife instrument to reduce the chance of having a seizure. Should a seizure occur, treatment will be immediately stopped. Should the patient have a severe seizure, treatment may be discontinued and resumed on a different day using software to merge different MRIs from respective days. This never occurred in the 30 patients in the Pilot Trial, but could occur with the 117 patients in the current trial.

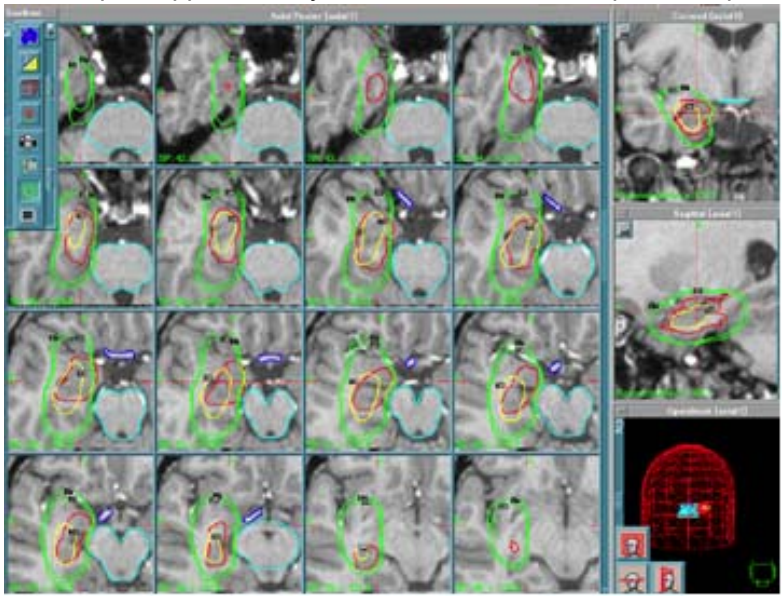


Figure 1. GK treatment planning session.

After treatment, the stereotaxic frame will be removed from the patient's head, small dressings will be applied to the skin puncture sites, and the patient will be

observed until clinical signs are stable (typically one to two hours).

An electronic copy of the final treatment plan for each subject will be stored at the Treatment Center by the Physicist. As these plans cannot have identifying information removed, the electronic copies will be stored on CDROM in a locked cabinet within the Study Center. Based on experience from the Pilot Trial, it is expected that there will be slight variations in radiosurgical treatment between subjects and between Treatment Centers. Variations will include volume of treatment, number of isocenters, maximum dose to amygdala and hippocampus. In addition, some centers produce treatment plans by outlining a "target" which is "filled" while others create an isodose plan that covers the appropriate anatomy. Although these differences did not influence outcome in the Pilot Trial, these parameters will be followed.

6 TEMPORAL LOBECTOMY

The surgeons who perform ATL will have to present documentation that they have performed at least 25 lobectomies at their current location in order to be "certified" to perform surgery in this trial. For those who do not meet these criteria, a selected member of the Surgery Committee will visit the site and observe this surgeon perform one lobectomy outside the trial. The surgeon must demonstrate appropriate surgical techniques including resection of medial temporal structures that would meet criteria in this trial. After this certification process is complete, the surgeon will be able to perform temporal lobectomies in this trial. It is impractical and should not be necessary to have on-site monitoring of all temporal lobectomies in the trial. If the post-operative MRI indicates an inadequate resection of tissue (See: Post-Temporal Lobectomy MRI Verification form below), a selected member of the Surgery Committee will discuss this with the surgeon involved and possibly observe an additional operation out of the trial based on recommendations of the Surgical Committee. This will be done to rectify any potential advantage of RS which can be monitored prior to treatment. Two such protocol violations at the same treatment site will result in the site being considered for discontinuation from the trial.

Patients who are randomized to ATL will be admitted to the hospital on the same day as their operation is scheduled. They will have the typical pre-surgical evaluation by members of the anesthesia team. The temporal lobectomy will be performed under general anesthesia. The superior temporal gyrus will be resected to a minimal degree (typically between one and two cm) and the middle and inferior temporal gyri will be resected to approximately three cm. Surgeons will use their experience and judgment based on individual anatomical variation. The minimum amount of lateral temporal cortex required to perform an aggressive resection of medial temporal structures will be performed. The temporal portion of the amygdala and the anterior two to three cm of the hippocampus will be resected. In addition, nearby entorhinal cortex will be removed in a fashion typical for amygdalo-hippocampectomy. Surgeons have agreed to perform a strictly anatomical resection in order to provide uniform procedures from patient to patient. This technique is one used at many epilepsy surgery programs and is identical to the protocol developed for a recent multi-center clinical trial (ERSET). The study will not attempt to control whether patients receive antibiotics, a copy of the patient's operative report and discharge summary will be made, identifying information will be removed and the subject's study number will be added to every page of every document. These data must be transmitted to the UCSF Study Center via upload to the Study database within one month of treatment.

Post-Temporal Lobectomy MRI Verification (sample: official copy in computerized CRF)

Pt ID # _____ Pt Initials: _____

Review Date: _____/_____/_____

Post-Temporal Lobectomy MRI Verification Form

Form to be completed by Neurosurgery Steering Committee member, upon receipt of study subject's post-op MRI and Operative report. If resection deemed inadequate, the treating neurosurgeon, Site PI, and Study PIs will be notified by Michael McDermott, MD.

Resection

Lateral temporal cortex resection extent: ____cm

Adequate resection of amygdala: ____Yes ____No

Hippocampus resection extent: ____cm

Parahippocampal gyrus/uncus resection extent: ____cm

Overall adequate resection **YES NO***

* If no, explain

Radiological adverse event

Injury/infarction of nearby cortex ____Yes ____No

Remote injury/infarction ____Yes ____No

Other significant abnormality ____Yes* ____No

*specify: _____

If deemed inadequate resection
Treating neurosurgeon notified on: Date: _____/_____/_____
Site PI notified on: Date: _____/_____/_____
Study PI notified on: Date: _____/_____/_____

7 POST-TREATMENT FOLLOW-UP

Post-treatment follow-up

All patients will be followed for a minimum of 3 years with the primary outcome measure defined as freedom from seizure for 12 consecutive months (25-36). Thus, all patients will have an identical follow-up period. All subjects will be followed closely for the 24 months leading up to this period, with special attention to adverse events and safety monitoring. The following data will be collected at each of these follow-up visits (Table 2).

Table 2. Schedule of postoperative data acquisition

	Post Op 3 mos	Post Op 6 mo	Post Op 9 mo	Post Op 12 mo	Post Op 15 mo	Post Op 18 mo	Post Op 21 mo	Post Op 24 mo	**Telephone 1, 25, 26, 28, 29, 31, 32 , 34, 35**	Post Op **27 mo**	Post Op **30 mo**	Post Op **33 Mo**	Post Op 36 mo
Review of Seizure Diaries	X	X	X	X	X	X	X	X		X	X	X	X
Focused Neuro Exam	X	X	X	X	X	X	X	X		X	X	X	X
HVLT-R		X	X	X	X	X	X	X					
Review of Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Formal Visual Fields Exam								X					
MRI	X (TL)			X (RS)				X (RS)					X (RS)
Neuropsych/ verbal memory battery				X				X					X
QOLIE-89	X			X				X					X
QOLIE-10		X	X		X	X	X			X	X	X	
Actual Life Changes In Epilepsy	X	X	X	X	X	X	X	X		X	X	X	X
Telephone Follow-up									X				
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X
Universal Billing - 92	X	X	X	X	X	X	X	X		X	X	X	X
Out Patient Billing	X	X	X	X	X	X	X	X		X	X	X	X

Data from these visits is to be transmitted to the UCSF Study Coordinating Center via upload to Study database.

1. *History, focused neurological examination, medication review and Hopkins Verbal Learning Test-Revised (HVLT-R).* Case report forms (CRF) standardize the evaluation of anticipated adverse events for symptoms such as headache, changes in seizure status or mood, and anti-epileptic medication and corticosteroid use. Treating physicians will be asked to maintain patients on stable doses of medications throughout the study. However, if it is thought to be in the best interest of the patient, changes in dosage or type of anti-epileptic medication will be allowed during the follow-up period, and such changes will be

captured on the CRFs.

To monitor for clinically significant adverse events, cranial nerve function, visual fields (office confrontation only with referral for formal visual field testing if a new deficit is detected), extra-ocular movements, motor examination and sensory examination will be evaluated with a standardized neurological examination.

2. *Review of seizure diaries and central adjudication.* Patients will be given monthly Seizure and Healthcare Utilization Diaries and instructions on how to complete them. Patients will be asked to record, on a daily basis, any seizure activity, including the number of seizures and types of seizures. To prevent bias in seizure counting, we specify a diary review protocol outlined below.

2a. At each study visit the study coordinator will remind the patient to be sure that all seizure activity and healthcare utilization information has been recorded on their study *Seizure and Healthcare Utilization Diaries* before handing them in. The study coordinator will review for legibility of entries only, and if illegible, ask the patient to clarify in a content-neutral fashion. The diaries will then be given to the blinded neurologist.

2b. The blinded neurologist will review the *Seizure and Healthcare Utilization Diaries*, assessing for compliance with coding. If the entries are ambiguous with respect to coding, the blinded neurologist will instruct the patient, in a content-neutral fashion, to comply with the seizure descriptions/coding noted on their calendar. Once the patient has edited the diary for clarification, the diary is "frozen" and the blinded neurologist then records the types of events and total number of each event directly on to the Seizure Frequency and Classification CRF. This CRF also requires the blinded neurologist to classify each event type (simple partial seizure, complex partial seizure, etc).

We anticipate that some patients will report the occurrence of a new event type during the course of the trial. In this circumstance, the blinded neurologist will review the written description of the event provided by the patient and discuss this event with the patient and then classify the new event accordingly. We encourage the blinded neurologist to focus on the best seizure classification according to his/her judgment, based on the description provided.

To reinforce the robustness of the seizure diary as an unbiased reflection of seizure outcome, seizure diaries will be subject to review by the central adjudicator. There are two conditions which will flag a diary for review.

First, all diaries are subject to review by the central adjudicator at the time of enrollment for the purpose of determining that the classification of event types, as described in the enrollment "Seizure Classification and Frequency" CRF, are adequately characterized in terms of symptoms. Event descriptions found lacking will be discussed between the central adjudicator and the Treatment Center PI for resolution and editing.

Second, after treatment, the patient may add an event type or the "blinded neurologist" may add or edit an event type (identified by a code letter within the seizure diary") based upon the interview with the patient. For example, if a patient self-identifies a new event of "déjà vu" as a simple partial seizure, but the blinded neurologist, based on the patient's symptoms, changes it to a complex partial seizure, the diary is "flagged" for central adjudication.

"Flagged" diaries will be reviewed by the central adjudicator. The adjudicator will be blinded to the treatment arm of the patient. The adjudicator will indicate his agreement or lack of agreement in event identification and seizure classification. This "second opinion" will be tracked independently with outcome statistics at study's end calculated independently.

3. *MRI.* ATL subjects will have a MRI performed at the three-month follow-up visit. RS patients will have a MRI when there is a report of (1) significant new headaches beginning with the six-month follow-up visit; (2) a clinically significant change in seizure type or frequency. If neither criterion occurs, an MRI will be obtained at the 12 month follow-up. Any subject who shows significant signs of radiation change (evidence of edema and mass effect) will have a repeat MRI scheduled for one month following the previous study. These studies will be repeated until there is substantial resolution of symptoms and radiological changes. These criteria were developed from experience during the Pilot Trial. All subjects treated with radiosurgery will have an MRI obtained at 2 years and 3 years following treatment. Any MRIs obtained for any reason will be sent (CDROM) to the UCSF Study Center for independent review by Study Center Radiologists.

4. *Other safety monitoring*. Based on the information gained in the Pilot Trial, guidelines for the use of corticosteroids (dexamethasone) in the treatment of postsurgical headaches stemming from edema have been developed and are listed below. In the Pilot Trial, most patients who required steroids could be tapered off within six weeks. This is slightly longer, but similar to the use of steroids following temporal lobectomy at most centers (typically 3-4 weeks). In addition, the Study PIs, Dr. Barbaro and Dr. Quigg are available for consultation with treating physicians involved in this study regarding steroid usage and guidelines.

Recommended guidelines for dexamethasone use in treatment of edema

With development of significant brain edema on MRI and severe new-onset headache, clinicians are advised to follow a six week protocol.

Week 1-2: Dexamethasone 2 mg po TID x 2 weeks, and evaluate clinical response;

Week 3-4: With clinical improvement, reduce dexamethasone to 2mg po BID x 2 weeks;

Week 5: Re-evaluate clinical response and MRI (if clinically indicated to follow brain edema). If edema improved and if clinically stable or improving, continue taper at dexamethasone 1 mg po BID x 3 days then decrease to dexamethasone 0.5 mg po BID x 4 days;

Week 6: Dexamethasone 0.5 mg po QD x 3 days, then decrease dexamethasone to 0.5mg po QOD x 3 days, then discontinue.

All subjects will have formal visual field assessments *(Humphrey 120 point exam)* at 2 years following treatment in order to assess and compare the visual morbidity of these two treatments in a homogenous group of patients.

5. *Neuropsychological/QOL battery.* Neuro-cognitive outcome measures are obtained at two sites. Major neurocognitive testing will occur at each treatment center's neuropsychological laboratory at baseline and on postoperative annual visits. QOL surveys and other secondary outcome data are obtained during standard clinic visits (Table 2).

Postoperative neuropsychological battery tests are obtained by "blinded" neuropsychology staff. The one-year assessment will be important as an early measure of toxicity and will also provide follow-up information in the cases where two-year data are not available (drop-out for any reason). Site neuropsychologists will perform standard administration procedures in order to ensure conformity in testing technique.

The study neuropsychologist (Broshek) will review neuropsychological data on a monthly basis. Any evidence of unusual scores (outside of the expected range) will trigger a query to the site neuropsychologist for protocol scoring review. The study neuropsychologist will be available for consultation to site neuropsychologists through the study to discuss administration, scoring, or other neuropsychological issues related to the study.

8 NEUROPATHOLOGY

Tissue specimens obtained from temporal lobectomies will be mailed via Fedex (or equivalent) directly to the University of California at San Francisco using the following address:

UCSF Department of Pathology, Neuropathology Division
Room M551, 505 Parnassus Avenue
San Francisco CA, 94143-0102
Phone: 415-476-5236
Attn.: Gretchen Werner, administrative assistant.

Receipt of specimens will be recorded in the electronic database and the specimens will be taken to the Neuropathology office. Dr. Tarik Tihan will then review the neuro-pathological findings and enter data into the electronic database using the form on the next page. After review, tissue specimen slides will be returned to the subject's treatment site study coordinator.

BARBARO et al.

RADIOSURGERY vs TEMPORAL LOBECTOMY in PATIENTS with CLINICALLY DIAGNOSED MESIAL TEMPORAL LOBE EPILEPSY with HIPPOCAMPAL SCLEROSIS (MTLE/HS)

PATHOLOGY EVALUATION FORM

Name= _____ Gender= ○ M ○ F Date of Birth = _____

STUDY CENTER = _____ Date of Surgery = _____

PATIENT ID NO = _____

SPECIMEN LOCATION (check ALL that apply)

R / L

- ○ Medial Temporal Lobe part_____
- ○ Lateral Temporal Lobe part_____
- ○ Hippocampus part_____
- ○ Amygdala part_____
- ○ Deep White Matter part_____
- ○ OTHER (specify) _____
- ○ OTHER (specify) _____

HISTOLOGICAL FEATURES	LOCATION	SEVERITY		
		Severe	Moderate	Focal
GLIOSIS		S	M	F
		S	M	F
		S	M	F
LOSS OF PYRAMIDAL NEURONS	○ CA1	S	M	F
	○ CA2	S	M	F
	○ CA3	S	M	F
	○ CA4	S	M	F
DENTATE NEURONS	Loss	S	M	F
	Dispersion	S	M	F
CORPORA AMYLACEA INCREASE		S	M	F
		S	M	F
DYSPLASTIC FOCI	○ NO ○ YES(specify)			
OTHER FINDINGS (describe)				
IMMUNOHISTOCHEMISTRY	ANTIBODY	INTERPRETATION		

9 RADIOLOGY PROTOCOL

The recommended protocol for pre-treatment and follow-up MRI is designed to maximize consistency of diagnosis and longitudinal follow-up across study centers. Pre-treatment imaging must allow for confident diagnosis of unilateral MTS and exclusion of dual pathology, such as bilateral MTS or co-existing gray matter heterotopia, neoplasm, or cortical dysplasia. Post-treatment imaging should be performed using an identical protocol in order to allow for (1) characterization of temporal lobe resection in subjects treated surgically, (2) assessment of radiation effects in subjects treated with radiosurgery, and (3) detection of complications associated with either treatment. For retrospective data analysis, it is particularly important that high image quality (spatial resolution, scan time, contrast, and artifacts) be consistently obtained across different scanner platforms and at different ROSE study centers.

The following sequences should be obtained *at either 1.5T or 3T* on a *GE, Siemens or Philips commercial MRI scanner*:

1) **3-plane localizer**, or if not available, axial localizer
2) **High-resolution fast spin echo (FSE) T2 (medial temporal lobes),** non-overlapping slices of maximum thickness 3 mm from the temporal poles through the ventricular atria
3) **Axial FSE T2 (whole brain)**, no thicker than 5 mm slices overlapping by 50%
4) **Coronally-acquired 3D inversion recovery T1 (whole brain)** with maximum slice thickness of 1.5 mm, suitable for reformatting in any orientation
5) **Coronal T2 FLAIR (whole brain),** non-overlapping slices of maximum thickness 3 mm
6) **Coronal gradient echo (whole brain)**, overlapping slices of maximum thickness 5 mm
7) **Axial and coronal diffusion (whole brain)**, non-overlapping slices of maximum thickness 5 mm
8) **Axial and coronal gadolinium-enhanced T1 (whole brain, for follow-up of gamma knife cases),** non-overlapping slices of maximum thickness 5 mm

IMPLEMENTATION NOTES

- Coronal sequences should be prescribed perpendicular to the longitudinal axis of the hippocampal body, and axial images be obtained orthogonal to this axis
- Whole brain sequences must be covered without image wrap
- When possible, 3T MRI is preferable to 1.5T MRI (note that the same voxel resolution should be used at both 1.5T or at 3T)
- It is desirable that imaging be performed using a multichannel phased array coil with or without parallel imaging (ASSET, ARC, SENSE)
- When preferred by individual sites, newer 3D FLAIR techniques (CUBE, VISTA, SPACE) may be used in lieu of conventional multi-slice FLAIR
- PROPELLER T2 and FLAIR images may also be substituted depending on local preferences
- All 3D sequences should be reformatted in axial, coronal and sagittal planes
- **Gadolinium-enhanced T1 sequences are required following gamma-knife treatment**

PROTOCOL EXAMPLE (UCSF, GE EXCITE HD 14.x)

SEQUENCE	TIME	IMAGING OPTIONS	TR	TE	TI	FLIP	ETL	BW	FOV	SLICE / SKIP	MATRIX	NEX
FMPIR COR	6 MIN	VB	5000	120		90	16	16	22x16	3/0	512x256	2
FSE T2 AX	4 MIN	FC, VBW	5850	100			17	31	22	3/0	384x384	1
3D-SPGR COR	8 MIN	FC, ZIP2	36	MIN		35			22X22	1.2/0	230x230	1
COR FLAIR	8 MIN	FAST, IR, VBW, 2D	10000	140	2200			16	22x16	3/0	256x192	1
MPGR COR	4 MIN	FC	787	25		20			22x16	5/0.5	256x192	1
DIFFUSION AX	1 MIN	VBW, EDR, EPI	10000	MIN		90	1 shot	167	36x27	5/0	256x128	1
DIFFUSION COR	1 MIN	VBW, EDR, EPI	10000	MIN		90	1 shot	167	36x27	5/0	256x128	1
GAD AX	5 MIN	FC	600	MIN		90			22x16	5/1	256x192	2
GAD COR	5 MIN	FC	600	MIN		90			22x16	5/1	256x192	2

All MRIs obtained during the course of this study are to be forwarded to UCSF for review. A copy of all MRIs with
report on CD will be mailed via Fedex (or equivalent) directly to the University of California at San Francisco
using the following address:

QUIPC
UCSF Department of Radiology
China Basin Landing
185 Berry Street, Suite 350, Lobby 6
San Francisco, CA 94107

Receipt of MRI CD's will be recorded in the electronic database and the scans will be forwarded to Steering
Committee member(s) for review.

10 NEUROPSYCHOMETRIC PROTOCOLS

BRIEF SUMMARY OF NEUROPSYCHOLOGICAL PROCEDURES

Neuropsychological Testing Procedures

A neuropsychology specific manual of operations will be provided to all sites. The purpose of the manual will be
to clearly delineate specific test administration instructions, specific normative databases, and to otherwise
standardize all procedures and anticipated scenarios that might occur as part of the neuropsychological assessment, including assessment of patients with English as a second language.

In addition, the study neuropsychologist, Dr. Broshek, will be available for consultation to site neuropsychologists throughout the study to discuss administration, scoring, or other neuropsychological issues related to the study.

Neurocognitive Tests

The following tests were chosen to evaluate neurocognitive functioning based on their well-established validity and common use in Comprehensive Epilepsy Programs as part of Phase I epilepsy presurgical evaluations:

- **Wechsler Abbreviated Scale of Intelligence** [Wechsler Abbreviated Scale of Intelligence Manual.
San Antonio, TX: The Psychological Corporation; 1999.]

- **Boston Naming Test** [Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test. 2nd ed. Philadelphia: Lippincott Williams; 2001.]

- **Rey Complex Figure Test** [Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. Archives de Psychologie 1941; 28: 286-340.

- **Brief Visual Memory Test-Revised** [Benedict, RHB. Brief Visuospatial Memory Test-Revised. Odessa, FL: Psychological Assessment Resources; 1997.]

- **California Verbal Learning Test** [Delis DC, Kramer JH, Kaplan E, & Ober BA. California Verbal Learning Test. San Antonio, TX: The Psychological Corporation; 1987.]

- **Wechsler Memory Scale-Third Edition, Logical Memory I & II subtests [**Weschler D. *The Wechsler Memory Scale–III manual*. San Antonio, TX: The Psychological Corporation, 1997.

- **Trail Making Test, A & B** [Reitan R. Trail Making Test Manual for Scoring and Administration. Tucson, AZ: Reitan Neuropsychology Laboratory; 1979, 1992.]

In addition, the following test was added due to its utility in further refining language assessment in patients with
temporal lobe epilepsy:

- **Auditory Naming Test** [Hamberger, MJ, Seidel, WT. Auditory and visual naming tests: Normative and patient data for accuracy, response time, and tip-of-the-tongue. Journal of the International Neuropsychological Society, 2003; 9: 479-489.]

Mood
Depression and anxiety will be assessed using the measures listed below in order to produce continuous variables of mood state. We elected not to use diagnosis based measures/structured interviews because we felt that dichotomous variables (meets diagnostic criteria for a specific mood disorder or does not meet such criteria) would not provide
the finer gradations in mood fluctuation that we desired and that are possible with measures yielding continuous
variables.

- **Beck Depression Inventory-II** [Beck AT, Steer RA, Brown GK. Beck Depression Inventory. 2nd ed. San Antonio, TX: The Psychological Corporation; 1996].

- **Beck Anxiety Inventory** [Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. Journal of Consulting and Clinical Psychology 1998; 56: 893-897].

Quality of Life

- **QOLIE-89** [Devinksy O, Vickrey BG, Cramer J et al. Development of the quality of life in epilepsy inventory. Epilepsia, 1998; 39: 81-8].

Modifications for Spanish Speaking Patients

As some sites have a patient population that is 10-20% Hispanic, we have made the following modifications in order to include these patients in the trial:

Since the neuropsychological tests used in this study have been developed and validated for individuals for whom English is their primary language, modifications to the neuropsychological test battery will be required for patients who will need tests administered in Spanish.

The data from patients who are not fluent in English will not be used for Aim 2, but will be collected and evaluated in order to ensure the safety of these patients while participating in this trial.

The neuropsychological battery for patients whose primary language is Spanish is as follows and will require completion of modified neuropsychological testing case report forms for Spanish speakers (see example CRF's at the end of this section) :

Ponton-Satz Naming Test. [Ponton, M.O., Satz, P., Herrera, L., et al. (1996). Normative data stratified by age and education for the Neuropsychological Screening Battery for Hispanics (NeBHIS): Initial report. Journal of the International Neuropsychological Society, 2, 96-104.

Rey Complex Figure. [Ardila, A., Rosselli, M., & Rosas, P. (1989). Neuropsychological assessment in illiterates: visuospatial and memory abilities. Brain and Cognition, 11, 147-166.

WHO-UCLA Auditory Verbal Learning Test. [Ponton, M.O., Satz, P., Herrera, L., et al. (1996). Normative data stratified by age and education for the Neuropsychological Screening Battery for Hispanics (NeBHIS): Initial report. Journal of the International Neuropsychological Society, 2, 96-104.

Color Trails Test. [Ponton, M.O., Satz, P., Herrera, L., et al. (1996). Normative data stratified by age and education for the Neuropsychological Screening Battery for Hispanics (NeBHIS): Initial report. Journal of the International Neuropsychological Society, 2, 96-104.

The data from patients who are not fluent in English will not be used for Aim 2, but will be collected and evaluated in order to ensure the safety of these patients while participating in this trial.

The neuropsychological battery for patients whose primary language is Spanish is as follows and will require completion of modified neuropsychological testing case report forms for Spanish speakers (see example CRF's at the end of this section):

Modications for Patients with IQ < 70

Individuals with an IQ < 70 who meet criteria for enrollment after capacity determination and appropriate consent/assent will not receive the standard ROSE neuropsychological battery as the majority of those tests have not been normed on that population; they may have differential sensitivity to temporal lobe dysfunction for individuals with IQ < 70. Enrolled patients with IQ < 70 will be assessed with the Dementia Rating Scale (DRS) at baseline and yearly follow-up as an alternative neuropsychological assessment. The DRS is a screening battery that provides a Total Score and five subtests which include Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory. This measure has been validated for use with individuals of lower cognitive ability.

McDaniel, WF & McLaughlin, T. (2000). Further support for using the Dementia Rating in the assessment of neuro-cognitive functions of individuals with mental retardation. *The Clinical Neuropsychologist, 14* (1), 72-75..

Pt ID # _____ Pt Initials: _____

Visit Date: _____/_____/_____ Visit Type: Pre-Treatment Screening

Multi-Center Gamma Knife Study – Neuropsychological Data Sheet
SPANISH VERSION

Patient Demographics		
Date:	Age (years):	Years of Education:
Hand Dominance: R L Mixed		

Verification of Recent Medical Information Potentially Affecting Neuropsychological Testing		
Have you had had any conscious sedation or sleep deprivation (e.g., for EEG or imaging studies) within the last 24 hours?	Yes	No
Have you had a generalized tonic-clonic seizure within the past 24 hours?	Yes	No
Have you had a simple partial seizure within the past 24 hours?	Yes	No
Have you had a complex partial seizure within the past 24 hours?	Yes	No
Have you taken a PRN medication (e.g., a medication that you do not take on a daily basis) within the last 24 hours?	Yes	No
If yes, please indicate the medication(s) and dosage(s):		

Neuropsychological Test Data	
Ponton-Satz Naming Test (30-item version) Total raw score (0-30)	
Rey Complex Figure Test Copy raw score (0-36)	
Rey Complex Figure Test Delayed Recall raw score (0-36)	
WHO-UCLA AVLT Trials 1-5 Total score (0-75)	
WHO-UCLA AVLT Short Delay Free Recall raw score (0-15)	
WHO-UCLA AVLT Long Delay Free Recall raw score (0-15)	
WHO-UCLA AVLT Recognition Hits (0-30)	
Color Trails Test, Trial 1 – Total seconds to completion (0-300)	
Color Trails Test, Trial 2 – Total seconds to completion (0-300)	
Beck Depression Inventory (Spanish version) – Total raw score (0-63)	
Beck Anxiety Inventory (Spanish version) – Total raw score (0-63)	
QOLIE-89 (Spanish version) - Total score (0-100)	

Pt ID # _____ Pt Initials: _____

Visit Date: _____/_____/_____ Visit Type: Post-Op 12, 24, 36 Months

Multi-Center Gamma Knife Study – Neuropsychological Data Sheet
SPANISH VERSION

Patient Demographics		
Date:	Age (years):	Years of Education:
Hand Dominance: R L Mixed		

Verification of Recent Medical Information Potentially Affecting Neuropsychological Testing		
Have you had had any conscious sedation or sleep deprivation (e.g., for EEG or imaging studies) within the last 24 hours?	Yes	No
Have you had a generalized tonic-clonic seizure within the past 24 hours?	Yes	No
Have you had a simple partial seizure within the past 24 hours?	Yes	No
Have you had a complex partial seizure within the past 24 hours?	Yes	No
Have you taken a PRN medication (e.g., a medication that you do not take on a daily basis) within the last 24 hours?	Yes	No
If yes, please indicate the medication(s) and dosage(s):		

Neuropsychological Test Data	
Ponton-Satz Naming Test (30-item version) Total raw score (0-30)	
Rey Complex Figure Test Copy raw score (0-36)	
Rey Complex Figure Test Delayed Recall raw score (0-36)	
WHO-UCLA AVLT Trials 1-5 Total score (0-75)	
WHO-UCLA AVLT Short Delay Free Recall raw score (0-15)	
WHO-UCLA AVLT Long Delay Free Recall raw score (0-15)	
WHO-UCLA AVLT Recognition Hits (0-30)	
Color Trails Test, Trial 1 – Total seconds to completion (0-300)	
Color Trails Test, Trial 2 – Total seconds to completion (0-300)	
Beck Depression Inventory (Spanish version) – Total raw score (0-63)	
Beck Anxiety Inventory (Spanish version) – Total raw score (0-63)	
QOLIE-89 (Spanish version) - Total score (0-100)	

Assessing Patients for English as a Second Language (ESL)

In order to balance the goals of science and inclusiveness, the following patients can be included in the ROSE trial using the standard neuropsychology battery outlined in the Manual of Operations (MOP):

- Native English speakers from the U.S. or other English speaking countries
- Patients who learned English before age 5 and were educated in English

For patients who do not meet the above criteria:

- Spanish speaking patients will be evaluated using the neuropsychological battery for Spanish speaking patients detailed in the MOP. Their data will not be used in statistical analyses of neuropsychological data, but will be monitored for safety of the patient.

- Patients with a primary language other than English or Spanish (e.g., Hmong, Korean, etc.) can be included

in the ROSE trial. The neuropsychologist at that study site must assess the patient using whatever standard measures he or she would typically use for assessing post-lobectomy change in that population. Testing would
need to be repeated at yearly intervals (12, 24, and 36 months post-operatively) to monitor the patient's safety.
This data will not be used in statistical analyses of neuropsychological data, but will be monitored for safety of the patient.

  - If the site neuropsychologist identifies any significant decrement in the patient's neuropsychological performance post-treatment, an adverse event form must be completed.

Neuropsychology Blinding Protocol Guidelines

- Since the initial neuropsychological evaluations will be performed as clinical evaluations prior to study

enrollment, these evaluations will be unblinded as they are part of standard clinical care and will occur prior to randomization.

- If a patient is enrolled and requires additional testing as part of the baseline neuropsychological evaluation required by the ROSE protocol, the neuropsychologist and psychometrist should be blind to study condition for the additional baseline testing.

- Each subsequent neuropsychological evaluation conducted as part of the ROSE protocol should be blinded. For sites that have a neuropsychologist and a psychometrist, both should be blind to the patient's treatment condition.

- Neuropsychological study personnel (neuropsychologist and psychometrist) should refrain from asking the patient any questions about treatment, seizure remission, or course of symptoms as this might result in disclosure of information pertinent to treatment condition, resulting in unblinding.

- Study patients will be asked to wear hats and obscure their hair (e.g., long hair should be tucked up into the hat) during neuropsychological evaluation to prevent inadvertent visual cues regarding their treatment condition and to maintain blinding of the neuropsychological personnel.

- In the rare event that a more extensive clinical neuropsychological assessment is required due to a patient's postoperative complications, the neuropsychologist may need to be unblinded in order

to provide appropriate clinical care. In such rare situations, the study site should alert the study neuropsychologist (Broshek) or study neurologist (Quigg) prior to breaking the blinding. For those sites with a psychometrist, the psychometrist should still remain blind to the patient's treatment condition even in this circumstance.

Measures To Be Administered Post-Treatment by Blinded Neuropsychologist or Psychometrist*

- Wechsler Abbreviated Scale of Intelligence (WASI)
- Boston Naming Test
- Auditory Responsive Naming Test
- California Verbal Learning Test
- Logical Memory I & II subtests from the Wechsler Memory Scale-Revised
- Rey Complex Figure Test
- Brief Visual Memory Test-Revised
- Trail Making Test, Parts A & B
- Beck Depression Inventory-II
- Beck Anxiety Inventory
- For Spanish speaking patients only:
    - Ponton-Satz Naming Test.
    - Rey Complex Figure.
    - WHO-UCLA Auditory Verbal Learning Test.
    - Color Trails Test.

***** *Psychometrists must work under the direct supervision of a neuropsychologist*

Wada protocol guidelines

The below protocol is adapted from the MCG Wada Protocol (Medical College of Georgia, 1995). Note that the ROSE trial requires a reporting of a standardized rating of lateralization obtained by the MCG protocol. Memory testing via the MCG protocol is listed but is not mandatory.

As most epilepsy programs are aware, sodium amobarbital (Amytal) is often in short supply, leading to the use of other anesthetic agents (case series document the use of propofol, methohexital, or etomidate). We emphasize that the sole purpose of the Wada test in the ROSE trial is to lateralize language and to relay that information to the trial via a 5 point scale: left, left>right, bilateral, right>left, right. We suggest that, when sodium amobarbital is not available, an alternative intracarotid agent be substituted from the list above, based on the local experience of the treating clinicians. Protocols to measure memory or other functions are at the discretion of the treating clinicians.

ROSE Trial Lateralization Scoring

All centers will interpret the results of language testing and report the findings in the form of a 5 point lateralization scale (Patient screening worksheet CRF): (1) Left hemisphere dominance, (2) Left > Right hemisphere dominance, (3) Symmetric hemisphere dominance, (4) Right > Left hemisphere dominance (5) Right hemisphere dominance.

General

Testing is performed immediately following cerebral angiography, and both hemispheres are studied on the same day. Patients begin counting repeatedly from 1-20 with their hands held up and their palms turned rostrally and fingers spread. An injection of amobarbital sodium (or published replacements such as methohexital, propofol, or etomidate) is administered by hand over a 4-5 second interval via a percutaneous transfemoral catheter. Following demonstration of hemiplegia and evaluation of eyegaze deviation, the patient is requested to execute a simple midline command (e.g., "touch your nose"). Beginning approximately 30-45 seconds following injection, eight common objects are presented for 4-8 seconds each, and the object names are repeated twice to the patient. Examples of Wada memory items include a combination of ordinary household items (e.g., fork, mousetrap), small toys (e.g., troll), and plastic food (e.g., hotdog, pizza). At times, due to patient confusion, inattention, or non-responsiveness,

the patient's eyes are held open. Language is assessed in detail following presentation of memory items. Recognition memory of material presented during the procedure is tested after drug effects have worn off as demonstrated by return baseline language performance on all tasks described below, return of 5/5 strength, and absence of pronator drift, tactile extinction, asterixis and bradykinesia.

Language

Language rating is based upon performance on five linguistic tasks (viz., counting disruption, comprehension, naming, repetition, and reading). Although we have developed a formalized approach to calculate a language laterality ratio, this is for research purposes and is not routinely used clinically. Expressive Language/Counting. The expressive language score (0-4) is based upon disruption of counting ability at the initiation of the Wada test (4 = normal, slowed, or brief pause < ~20 seconds; 3 = counting perseveration with normal sequencing; 2 = sequencing errors; 1 = single number or word perseveration; 0 = arrest > ~20 seconds). We have adopted a period of speech arrest of this duration to insure that counting interruption is not due to acute generalized disruptive effects of the medication. If speech arrest occurs, patients are repeatedly urged to begin counting again starting with "1" since the more overlearned portion of the sequence will be less likely disrupted from generalized medication effects.

Comprehension: Simple comprehension is assessed after assessment of eye gaze deviation by requesting the patient to execute a simple midline command (e.g., “stick out your tongue"). Following object memory stimulus presentation, comprehension is more systematically assessed with a modified token test. The token test consists of four geometric shapes of different colors which are presented vertically to the subject's ipsilateral visual field. Comprehension is rated based upon the level of syntactic complexity in the command that is correctly executed: 1. "point to the blue circle after the red square," 2. "point to the red circle and then point to the blue square," 3. "point to the red square." A score of 3 is awarded for completion of a complex two-stage command with inverted syntax, a score of 2 reflects successful simple two-stage command, 1 is scored for one-stage commands and 0 if the subject cannot perform any commands.

Confrontation Naming: Two line drawings of common objects (i.e., watch and jacket) are presented and the subject is asked to name the objects and parts of the objects (e.g., watchband, collar). Performance is qualitatively scored on a 0-3 point scale. Repetition. Following object naming, the patient repeats phases (e.g., "No ifs, ands, or buts") and repetition is graded on a 0-3 rating scale. If unable to provide any response, the patient is asked to repeat "Mary had a little lamb." Reading. Patients are asked to read either "The car backed over the curb" or “The rabbit hopped down the lane." Performance is rated on a 0-3 point scale.

General Language Considerations: When language impairments are present, language stimuli are presented throughout the recovery phase to monitor drug effects. The time of complete language recovery is noted. The same or alternative stimuli as those employed during the initial assessment are used with the exception of repetition. Repetition is a very sensitive measure of mild language impairment, and additional repetition items such as "Methodist-Episcopal" and sentences from the Boston Diagnostic Aphasia Examination are used to monitor recovery (e.g., The spy fled to Greece). Positive paraphasic responses are considered the single strongest evidence of language representation in the hemisphere being studied.

Memory

A minimum of 10 minutes following drug injection is required prior to memory testing. Although free recall of object memory stimuli is obtained, interpretation of Wada memory performance is based solely on object recognition. Ipsilateral Performance. Each of the 8 objects is presented randomly interspersed with 16 foils, and forced choice recognition is obtained. One-half the number of false positive responses is subtracted from the number of objects correctly recognized to correct for possible response bias and guessing. Thus, the expected score in the absence of true recognition is 0.

Laterality Scores

Since Wada memory scores are used to assist in seizure onset lateralization by demonstrating lateralized dysfunction, the order of injection is randomized across subjects and memory results are interpreted in a blind fashion. To assess lateralized asymmetries, interhemispheric Wada memory difference scores (i.e., [left injection] - [right injection]) derived from corrected memory performances are computed; positive scores suggest left temporal lobe dysfunction and negative scores suggest right

temporal lobe impairment.

For the purposes of this study, treatment centers will abstract language dominance laterality according to the following scale: left dominance, left>right dominance, symmetric, right>left dominance, and right dominance.

General Memory Considerations

Fixed pass/fail criteria are not employed for memory performance following injection ipsilateral to the seizure onset. However, we generally require a score of at least 2/8 in order to not repeat the Wada memory assessment, and are more comfortable with scores of at least 3/8 correct. Asymmetries of at least 2 are interpreted as evidence of lateralized impairment, although greater asymmetries are interpreted with more confidence. As with the ipsilateral performance, the asymmetries scores are not considered absolute, and memory performance is always considered in the context of other clinical factors such as consistency of seizure onset or presence of a structural lesion such as tumor or hippocampal atrophy on MRI. Although asymmetries in the "wrong" direction are sometimes observed, when they are present, they are cause for particular concern and the procedure may be repeated bilaterally using a 75 mg dose and beginning on the side ipsilateral to the presumed seizure onset.

11 Treatment Cost Utility Analysis

The following describes how to collect information on health care utilization and transfer it to case report forms (CRFs) to support Aim 4 (Cost-Utility Analysis) of this trial.

1) Start-up Activities - Site PI and Coordinator
    a. Integrating Aim 4 into Informed Consent Form – Language is provided in the model informed consent form to reflect the fact that researchers will be requesting billing information from the hospital and clinic at the study site. This language may require modification at each site, but must clearly communicate to the subject the confidentiality and limited purposes of the data collection.

    b. Obtaining Permissions for Billing Data – Billing data must be obtained from neurology and hospital billing departments. The site PI should discuss the study with a senior financial administrator in the site hospital who has the authority to direct the billing departments to provide the data (e.g., Senior VP for Finance). Getting permission to obtain these data will be facilitated by making the following points:
    - Subjects will give informed consent to release billing data.
    - The institution will be assisting a federally-funded study.
    - If the study is successful, their institution will be able to provide a cost-effective alternative that their competitors may be less able to provide.
    - Institutional confidentiality about charges and costs will be maintained in the following ways:

    1) A 'Medicare' costing approach will convert hospital charges to costs, using publicly available information from Medicare cost reports. Charges will not be reported publicly. Proprietary cost- accounting information will not be requested.

    2) During data collection and analysis, institutional identifiers will be known only to the investigator charged with this component of the analysis who is not affiliated with any of the participating sites.

    3) Publications will report aggregate costs over general categories of care (e.g., inpatient vs. outpatient vs. medications) and periods of treatment (cf. Langfitt, JT, Neurology, 2007 for an example). No attempt will be made to analyze or report institution-, visit-, procedure- or admission-specific costs.

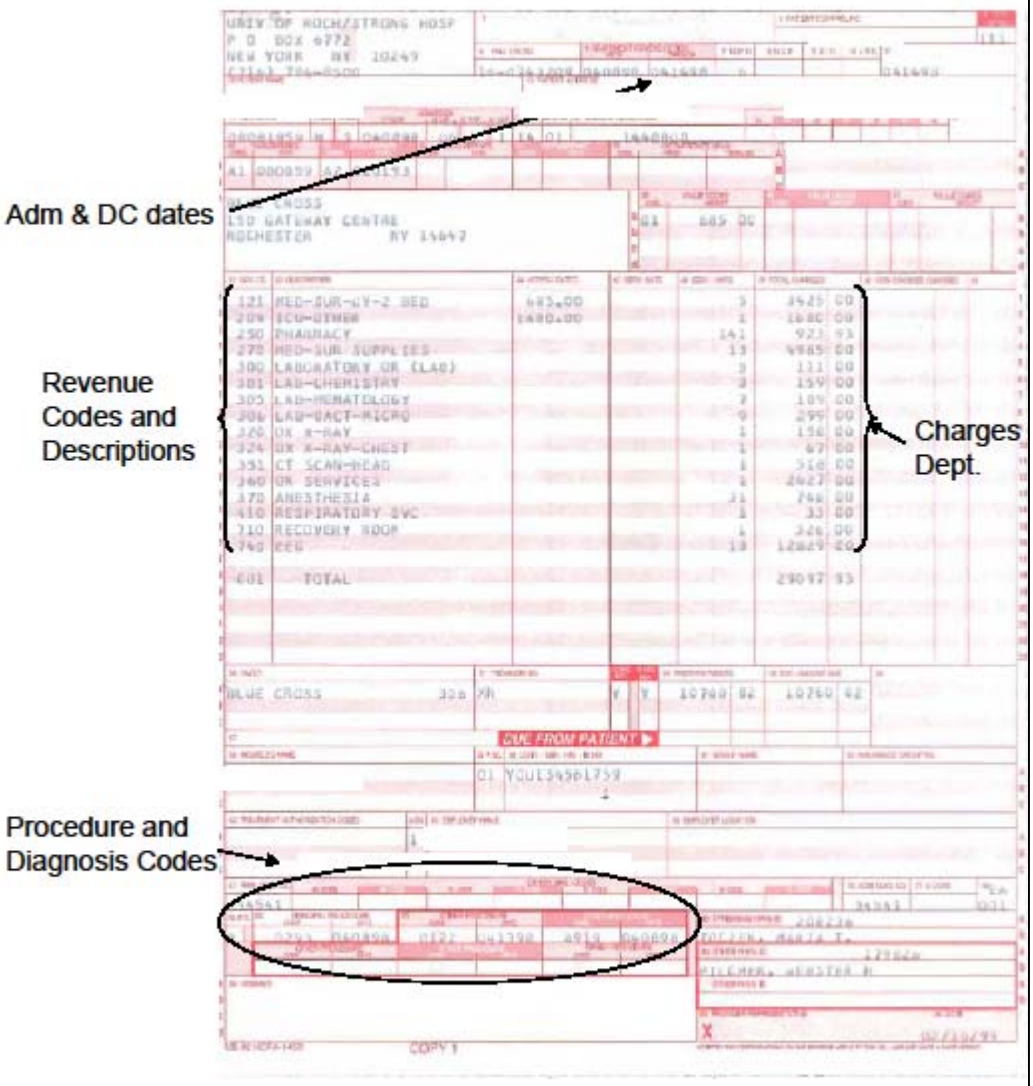
    4) All data will remain on a secure server and will not be shared with anyone outside the study.

5) According to Brandy Fureman of NINDS, if any information from this study is requested through a Freedom of Information Act application, the grant PI has an opportunity to redact portions of the information if it is considered proprietary or otherwise sensitive. NIH program staff can also redact additional information before anything is released.

c. Liaison with Billing Depts. Once the administrator agrees, they should introduce the project and the Site PI to the Inpatient and Outpatient Billing Department Directors. It is recommended that the Site PI communicate directly with these persons at this initial phase to ensure responsiveness. Cooperation should not be difficult to obtain, but may require diplomacy. Although they may not have dealt with this kind of request before, they will be highly familiar with the kind of data you will be requesting. The work involved for their staff is fairly trivial, but many billing departments do not see supporting research as within their mission and thus will view this as doing you a favor and a relatively low priority. Given all this, a collaborative approach with Billing Directors is highly recommended.

Explain to the Inpatient Billing Director that, on a quarterly basis, the site study coordinator will be providing a list of medical record numbers for currently enrolled subjects and dates of admission for all study-related admissions. (The purpose of providing dates of the study-related admissions is to prompt billing personnel if they miss a known admission.) The Billing Department is to provide the study coordinator with a paper copy of the UB-04 billing form for ALL inpatient admissions at the study-site hospital for ROSE-enrolled subjects (not just study-related admissions) during the previous quarter in a timely fashion (e.g., within two weeks). The UB-04 is a one-page, universal billing form that is used to report uniform data on charges, diagnoses and procedures to Medicare on all hospital admissions
and is familiar to all hospital billing departments. An annotated, sample UB-04 form (previously referred to as a UB-92 form) is provided below.

SAMPLE UB-92 FORM



A similar process should be followed with the director of billing for the outpatient neurology facility where the majority of clinical care and study visits will occur. The primary purpose of collecting outpatient billing data is to validate and provide back-up for utilization data recorded by the subject in the seizure diary. The Site PI will request information on all outpatient visits to this facility for each ROSE-enrolled subject on a quarterly basis. These data can be provided in the format that is most convenient for the persons providing and entering the data. The only information required is the subject identifier, date of service and 5-digit CPT code used to bill for the service.

Outpatient provider visits need to be obtained, at minimum. If information on procedure(s) (e.g., EEGs) is readily available from the same outpatient billing system, these may be included. If they are included, they should be included consistently throughout the trial at that site. If there is concern that they will not be provided consistently throughout the trial, they should be left out altogether.

d. Piloting Data Acquisition: Prior to enrollment of the first ROSE subject at the site, the coordinator should provide the outpatient and inpatient billing department with medical record numbers of 3-4 patients known to have accessed multiple inpatient and outpatient services in the previous quarter. After obtaining the data, they should confirm billing dates with information in the medical record. This activity should not require IRB approval, since no data will actually be collected for research purposes, but sites are advised to confirm this with their local IRB and obtain expedited approval for this activity, if needed.

2) Post-Enrollment Activities – Site Coordinator and Data Manager

a. Obtaining Billing data – Site-coordinators will obtain UB-04s and outpatient neurology billing records on a quarterly basis for all enrolled subjects, as described above.

b. Recording Utilization Data in Seizure Diaries – Subjects need to be instructed to record ALL episodes of health care for seizure-related and unrelated health problems (including study visits) in their Seizure Diaries, by assigning alphabetic codes to the dates when care was received. The codes are listed below, and refer to broad categories of care, as follows:

O = Outpatient Visit - any outpatient visit with a licensed doctor, nurse practitioner, or allied health professional (e.g, psychologist, physical therapist, etc.) for the purpose of providing care or explaining the results of tests, procedures, etc.
H = Hospitalization Overnight – any episode of care that required an overnight stay in an inpatient facility. Subjects should enter the letter H on each day in the Diary on which they spent the night in hospital (i.e., the first night is the night after admission and the last night is the night before the day of discharge).
L = Laboratory Test – any collection of bodily tissue (e.g., blood, urine, etc.) for laboratory analysis. Multiple collections on a single day at the same facility should be counted as a single episode, but collections at different facilities should be counted separately. For example, a visit to a neurologist during which blood levels are drawn should be recorded as 'O, L' in the Diary.
T = Other test, or procedure. Record all outpatient tests and procedures (e.g., MRI, EEG, visual field testing, radiation treatment), even if they occur as part of a visit recorded as 'O'. For example, a visit to a neurologist during which an EEG is also performed should be recorded as 'O,T' in the Diary. If the EEG is done by a technologist and the neurologist is not seen, then only record 'T'.
X = Dental Care – any visit to a dentist, orthodontist or other dental provider. Procedures performed during such visits are NOT coded separately.
Z = Emergency Department Care – any visit to an Emergency Department that does NOT result in a direct admission to a hospital for an overnight stay. If a subject is admitted directly from the Emergency Dept. without first leaving the facility, then only an 'H' should be recorded for that day. If a subject is discharged from an Emergency

Dept. and then returns to the facility to be hospitalized, both Z and H are recorded for that day.

Recording Work Time Lost due to Seizures or While Seeking Care –

At the outset of the study, subjects should be asked to identify the one person who most commonly takes them for their appointments. Information will be recorded about this person's age, gender and employment status (full-time, part time, not working for pay) on the Review of Seizure Diary case report form. Subjects should be instructed to indicate in the diary entry any hours that they and/or their caregiver lost from paid employment as a result of seizures, treatment-related symptoms (e.g., headaches, other treatment side-effects, convalescence) or having to seek care. Hours should be rounded to the nearest hour. Only hours lost from paid employment should be recorded for the subject first and then for the caregiver, identifying each of the numbers with 'SS' or 'CG' (see Worked Example, Section c.iii, below)

c. Completing Data Forms
   i. UB-04 CRF - A single CRF should be used to record data from a single UB-04 form. A completed example of a UB-04 CRF form using data from the Annotated UB-04 form on page 25 is included at the end of this section. The layout of the UB-04 form may be slightly different at your institution, but it will contain all the data required to complete the form. Round all charges to the nearest dollar. Include leading zeroes.
   ii. Diary and Outpatient Billing CRF- A single CRF can be used to record episodes from both the Seizure Diary and the outpatient billing data.
      1. For Seizure Diary data, enter the date from the diary and the corresponding alphabetic codes. NOTE: Alphabetic codes A-F designate seizure occurrence. Don't confuse these codes with the utilization of care codes (O, H, L, T, X and Z). If more than one code occurs on a single day, code each episode on a separate line. For overnight hospitalizations, enter the date of admission and the 'H' code, followed by the number of nights spent in the hospital. For example, for a subject admitted on 10/12/09 and discharged on 10/19/09, the corresponding record would read ' 10/12/09, H7'.
      2. For Work Hours Lost, enter the number of hours of paid work lost for the caregiver and subject (if any), as recorded in the diary. These can be entered on the same line as the episode of care. If there are Work Hours lost on days without an episode of care (e.g., staying home from work with a headache), enter zeroes for Diary/Billing/Study Visit CODE.
      3. For outpatient billing data, enter the date of service and the 5-digit, CPT code provided by the billing department. Enter zeroes for Work Hours Lost for these entries.

   NOTE: Because subjects will be recording in their diary outpatient visits to the study-site neurology clinic, there will be duplicate recording of visit information (one from the diary, one from the billing data). This double-counting is intentional and will be dealt with at the data analysis phase. It is designed to validate the diary methodology. Therefore, be sure to remind subjects to record ALL visits, regardless of site of care. Be sure to record BOTH billing information and diary information (only if it was recorded by the subject) for the same episode on the CRF. If you notice that a subject has failed to record visits in their diary for which billing data has been received, you should remind them at the next contact to record this information prospectively.

   iii. Diary and Outpatient Billing CRFs – Worked Examples – (see Seizure Diary and Outpatient Billing CRF Sample at end of this section)

10/1/98 – Subject 3123 has CPS at home on Sunday, recovers without seeking care – no health care or lost hours recorded on CRF for that day
10/2/98 – Subject has GTC at 1PM at work, wife leaves her work, to pick him up, calls neurologist and goes to have AED levels drawn at local lab. Subject and wife do not return to work, resulting in 4 hours of work lost for each of them.
10/4/98 – Subject has brief CPS at work, recovers uneventfully at work. No care sought, no hour lost from work.
10/5/98 – Subject and wife meet with study neurologist for an hour, missing two hours of work each. Labs are drawn. Billing data subsequently obtained from the Neurology Outpatient Billing. Department codes this as a High Complexity Follow-up (CPT code 99215). Hours lost are entered as zero on the line where the CPT code is entered to avoid double counting of work hours lost.
10/7/98 – Subject has GTC while attending sporting event, sent to ED by ambulance, discharged home. No work hours lost, as subject was not at work.
10/8/98 – Subject is electively admitted for three nights of EEG monitoring at study-site hospital and is discharged on 10/11/98. He misses four full days of work. Wife misses 2 hours on the 11th, picking him up at hospital and speaking with doctors. Costs of this admission to the study-site hospital will be captured separately on a UB-04 CRF and double counting will be addressed at the analysis phase.

SEIZURE DIARY

Patient ID# ___3123_____ Pt. Initials _____JTL__

Seizure Record *Neurologist to verify and classify seizure events/type at each visit. Describe the types of seizures you had since your last visit. List only one type of seizure per line. When recording the date and seizure type below, place the letter which corresponds to the seizure type that occurred:

A. _____GTC_____
B. _____CPS_____
C. _____
D. _____
E. _____
F. _____

Health Care Use Codes
O = Outpatient (Clinic) Visit
H = Hospitalization overnight
L = Lab test (e.g., drug levels)
T = Other Test/Procedure
X = Dental Care
Z = Emergency Room visit

Enter on each day – Total Number of Hours Lost from Paid Work due to Symptoms and Seeking Care (list Subject's and Caregiver's hours list separately)

Month: ___Oct_____ Year: ___1998___

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1 B	2 A L 4SS 4CG	3	4 B	5 O,L 2SS 2CG	6	7 A , Z
8 H 8SS	9 H 8SS	10 H 8SS	11 8SS, 2CG	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

Neurologist (Blinded) Signature: _____

Pt ID # __3123_____ Pt Initials: _JTL_____

Visit Date: 6/12/1998 Visit Type: Post-Op 36 Month

UB-04 (Universal Billing – 04) CRF

1) Subject ID ___3123_____ 2) Site ID __12_____

3) DOA (mm-dd-yy) _04_/__08_/_98__

4) DOD (mm-dd-yy) _04_/__14_/_98__

5) PP Code __0293 _____ 8) OP Code 3 _____

6) OP Code 1 __0122_____ 9) OP Code 4 _____

7) OP Code 2 ___8919_____ 10) OP Code 5 _____

11) PDX Code ___345.41_____

Rev Code Description Charge (round to nearest dollar)

12) __1_ _2__ _1_ MED-SURG-GY-2-BED__ __0_ _ 3_ _4__ _2__ _5__

13) __2_ _0__ _9__ ICU-OTHER __0_ __1_ _6__ _8__ _9__

14) __2_ _5__ _0__ PHARMACY_ _____ __0_ __0_ _9__ _2__ _4__

15) __2_ _7__ _0__ MED-SUR SUPPLIES____ __0_ __4_ _9__ _8__ _5__

16) __3_ _0__ _0__ LABORATORY OR (LAB) __0_ __0_ _1__ _1__ _1__

17) __3_ _0__ _1__ LAB-CHEMISTRY_____ __0_ __0_ _1__ _5__ _9__

18) __3_ _0__ _5__ LAB-HEMATOLOGY __0_ __0_ _1__ _8__ _9__

19) __3_ _0__ _6__ LAB-BACT-MICRO __0_ __0_ _2__ _9__ _9__

20) __3_ _2__ _0__ DX-X-RAY_____ __0_ __1_ _1__ _5__ _8__

21) __3_ _2__ _4__ DX X-RAY-CHEST __0_ __0_ _0__ _6__ _7__

22) __3_ _5__ _1__ CT-SCAN-HEAD_____ __0_ __0_ _5__ _1__ _8__

23) __3_ _6__ _0 OR-SERVICES_____ __0_ __2_ _6__ _2__ _7__

24) __3_ _7__ _0 ANESTHESIA _____ __0_ __0_ _7__ _6__ _8__

25) __4_ _1__ _0_ RESPIRATORY SVC___ __0_ __0_ _0__ _3__ _3__

26) __7_ _1__ _0_ RECOVERY ROOM_____ __0_ __0_ _3__ _2__ _6__

27) __7_ _4__ _0__ EEG_____ __1_ __2_ __8_ __2_ _9__

28) ____ ____ ____ _____ ____ ____ ____ ____ ____

29) ____ ____ ____ _____ ____ ____ ____ ____ ____

Practice: **ROSE Trial**
Patient Id:
Last Update:

ROSE Trial
Universal Billing

Any site hospitalization in past 3 months? ○ Yes ○ No

Day of Admission: _____ **Day of Discharge:** _____

Please enter leading 0's (when present) for all PP (Primary Procedure), OP (Other Procedure) and Dx codes.

PP Code: _____

OP Code 1: _____ **OP Code 2:** _____ **OP Code 3:** _____ **OP Code 4:** _____ **OP Code 5:** _____

Dx Code: _____

REV CODE	DESCRIPTION	TOTAL CHARGES (round to nearest dollar)
_____		_____
_____		_____
_____		_____
_____		_____
_____		_____

Add More

Signature: - Select a Physician - **Initials:** _____ **Date:** _____

Cancel

Seizure and Health Care Utilization Diary

Patient Instructions

On a daily basis, please record on the attached calendars the following information:

1. **Seizure Events**- Using the Seizure Descriptions and Codes listed below, record seizure code(s) and number of each event (s) that occurred on that day. For a new seizure/event, write out a detailed description of the event and record the number of these events on the calendar also. At your next Study appointment, your doctor will review this description with you and assign a code for that event type for you to use from now on should this new type of seizure recur.
2. **Healthcare utilization**- Using the Health Care Use Codes listed below; record each specific type of health care service(s) utilized on the day the visit or service was obtained. Put an "H" for every night you stay overnight in the hospital.
3. **Paid Work Time Lost** by study subject and/or designated caregiver due to seizures, treatment related symptoms, or seeking medical care- Using the codes below record the number of paid work hours lost, rounded to the nearest whole hour, by the study subject (SS) and/or designated caregiver (CG).

Seizure Descriptions	Health Care Use Codes
A.	O Outpatient (Clinic) Visit
B.	H Hospitalization overnight
C.	L Lab test (e.g., drug levels)
D.	T Other Test/Procedure
E.	X Dental Care
F.	Z Emergency Room Visit

Paid Work Time Lost by Study Subject and/or Caregiver: Record separately

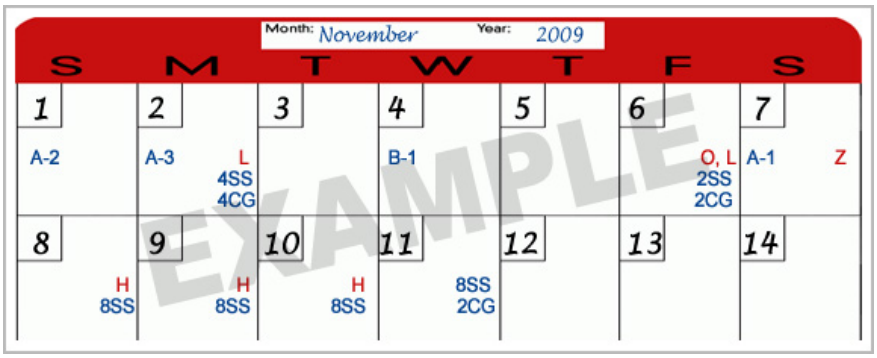
- Number of paid work hours lost by **Study Subject** (code: **SS**) due to symptoms and seeking medical care, rounded to the nearest hour, on each day
- Number of paid work hours lost by designated **Caregiver** (code: **CG**) due to symptoms and seeking medical care, rounded to the nearest hour, on each day. (Note: Designated Caregiver is the identified individual at the outset of the study that most commonly takes study subject to appointments and provides care).

Study Subject (SS) Employment status: Full time ☐ Part time ☐ Not working for pay ☐

Designated **Caregiver (CG)** Employment Status: Full time ☐ Part time ☐ working for pay ☐

Age of **caregiver** _____ yrs Gender of **caregiver** Male ☐ male ☐

Please record seizure types and



counts on left side. Health Care Use codes are placed in Red on the right side. Place the Time Lost codes underneath the Health Care Use codes on the right. For example, on Monday the 2nd, there were 3 Type A seizures, a Laboratory Visit, and 4 work hours lost by the Study Subject and the Care Giver.

The Treatment Cost Utility Analysis aim is being directed by John Langfitt, Ph.D. at the University of Rochester, Rochester, NY. If you encounter difficulty in obtaining necessary cost analysis data or transposing data onto appropriate forms, please direct inquiries to Dr. Langfitt at john_langfitt@urmc.rochester.edu or call 585-275-9495.

12 DATA ACQUSITION, SUBMISSION AND MONITORING

Data and safety monitoring plan

The trial will utilize the VisionTree Optimal Care ™ (VTOC) system provided by VisionTree Software based in San Diego, CA. The VTOC system is a HIPPA-secure 128-bit SSL encrypted database with 7 levels of roles/permissions access. VTOC contains a web-based system for global trial administration access to improve the compliance and accuracy of data collection, validation and reporting. VTOC is compliant with the 21CFR part 11 statistical process control system and provides messaging and reminder capabilities to alert study participants of appropriate follow up protocol.

The CRF's contained in our MOP will be converted into electronic interactive forms within VTOC. Selected individuals from each treatment site will have access to their own VTOC account with a unique secure password. A record will be available to track every entry, including changes in data that indicates the individual making the entry along with the date and time the entry was made. Study patients will be de-identified and randomized (if accepted) using a study number based on the treatment center code. Treatment centers will only have access to their data and will be prompted by alerts for ongoing protocol compliance. Data from all treatment sites will be centralized and accessible in real-time by the Database Coordinator and Committees for monitoring and ensuring compliance. Customized report templates will be utilized by the Database Coordinator for ongoing review and analysis.

Study site staff members at individual treatment sites will access their own data queries via the secure web site and resolve them in a timely manner. An audit trail of changes to the data is automatically produced.

Adverse events will be tracked through the VTOC system by way of dynamic survey logic and email/database alerts. Fields within surveys will include logic for triggering email alerts when data falls outside of normal parameters. Both email alerts and database alerts can be routed to appropriate individuals for follow up.

Data management and quality assurance

All Treatment Centers during the six-month start-up period will receive training on how to use the VisionTree Optimal Care™ database system by a VTOC Clinical Applications Manager. VisionTree Software will provide ongoing support to the study sites on the VTOC system as needed via web and phone. Mariann Ward, our Data Management Coordinator, will also be available to assist treatment centers via telephone and E-mail consultation who have questions regarding data gathering, recording, and transmission. John Langfitt will also be providing educational support regarding data acquisition and form completion, especially as it pertains to our cost analysis and quality of life data.

Quality control of data collection and entry will be as follows: Each Treatment Center will be responsible for an appropriate sample audit to compare data forms with on-line database entries for each subject. The Treatment Sites will perform a 100% audit of key data fields and an additional audit on a random sample of all data fields to compare information on the case report forms, subjects medical records, and source documents to that which is in the database on a per patient/clinic visit basis. Key data fields will include all Adverse Events, and the following treatment variables: radiosurgical dose

planning (100% oversight of this process is based on transfer of treatment plan to the Study Center on the day of treatment), copy of the operative report for temporal lobectomy, and all seizure counts. Actual seizure calendars will be kept at the Treatment Centers for potential review of the source data if needed.

The PI from the Treatment Centers will inform the Study Center Data Management Coordinator of any identified errors and correct accordingly. In addition to the onsite internal audit performed on a per patient /clinic visit basis, we will ask that each center perform this audit explicitly with the enrollment of their patients and on a bi-annual basis with all enrolled subjects thereafter. We will ask for written verification that this bi-annual audit has taken place.

Every radiosurgical procedure will require transmission of the treatment plan to the Study Center, on the day of treatment, and an electronic copy of the final treatment plan for each subject will be stored at the Treatment Center by the Physicist. As these plans cannot have identifying information removed (built into the Gamma Plan software), the electronic copies will be stored on CD ROM in a locked cabinet within the Study Center. For temporal lobectomy study patients, a copy of their operative report and discharge summary will be made, identifying information will be removed and the subject's trial number will be added to every page of every document. An electronic copy of these data will be uploaded to the database within one month of treatment. These data will be used by the Chair of the Surgery Committee, along with review of the postoperative MRIs to assess adequacy of surgical resection.

Relevant data will be transmitted to the Committees responsible for oversight. Neurological data (seizure, medication and neurological examination) will be transmitted to the Neurology Committee. Surgical data including operative reports, discharge summaries, post-operative MRI and adverse events will be transmitted to the Neurosurgery Committee. Radiological studies will be transmitted to the Neuroradiology Committee. Neuropsychological data will be transmitted to the Neuropsychology Committee. The Study Neuropathologist will complete a pathology specific case report form (see page 20) for each pathology specimen received and reviewed. Committee chairs will report to the Steering Committee and documentation that these reviews take place will be kept by the Principal Investigator.

Adverse events can be tracked relatively easily using the VTOC system. The fact that an adverse event is reported will trigger communication (e-mail notification) with the appropriate individuals. The Principal Investigator and the Chair of the relevant committee will also receive notifications. In addition, Principal Investigators at each Treatment Center will be responsible for notifying the Study Principal Investigator of any serious adverse event within 48 hours of recognition (e-mail notification preferred as this generates a transmittable document). The Study Principal Investigator will be responsible for notifying the Independent Medical Monitor and Chair of the DSMB and transmitting all written material related to the event for DSMB review. The DSMB Chair will determine whether an urgent review of the event is required and proceed accordingly. The DSMB will consider suspension of enrollment should there be sufficient numbers of serious adverse events in either arm of the study

Study Wide Website Communications

Most communication and problem-solving regarding data management issues will occur through a central website provided by the data management system. The private, secure website provides access to a study-wide directory with phone numbers, fax numbers and e-mail addresses of all study sites and core labs. It serves as a central repository for study documents including the operations manual, meeting and conference call minutes, all-site emails, and all required CRFs. The website also includes dynamic reports reflecting the data as it is acquired, and provides the central means by which error-checking and queries are processed. In all cases, account permissions are carefully controlled such that site personnel logging into the website will have access to all central functions, but will only be able to access data reports and process queries relevant to their own site. This portal will also serve as a means of communicating progress and tips for recruitment and generalized communication for both study center and individual treatment centers.

Computer and Data Security

A high level of data security and redundancy are built into the VTOC system with co-location data store sites behind multiple firewalls and encrypted databases. Physical technologies include an F5 Load

Balancer and Cisco Firewall. Software technologies includes 128-bit SSL 3rd party verification, command line and basic virus scanning, audit logs, secured biometric access to the data centers and encrypted databases. VisionTree co-location data storage centers are SAS-70 compliant and located in San Diego, CA and Kansas City, MO. A Disaster Recovery and Notification System are in place in case of any issues with a hot swappable setup and backup system ready.

Data and Safety Monitoring Board (DSMB)

A DSMB will be formed based on NIH Guidelines. Regular reports will be provided and meetings held (physical or telephone conference as deemed appropriate by the DSMB) to monitor the conduct of the trial. The DSMB will determine the frequency of these meetings; a six-month interval is expected.

Adverse Event Monitoring

Serious adverse events will be reported within 48 hours of occurrence to the Independent Medical Monitor (IMM), the PI and to the Committee Chair of the relevant committee. Independent monthly conference calls will be held by the Steering Committee and the IMM to facilitate discussion and transfer of information regarding adverse events. The DSMB (see proposed composition above) will be notified within 48 hours of any serious adverse event (SAE). Serious adverse events include:

- new neurological deficits (other than expected visual field abnormalities)
- need for hospitalization for treatment-related event (determined initially by IMM)
- status epilepticus
- unusual radiological findings (stroke, hemorrhage).

Enrollment in the trial will be temporarily suspended if two SAEs considered by the DSMB to be treatment related occur within one arm of the study. The decision on resumption of the trial will depend on the nature of the events leading to trial suspension based on recommendations by the DSMB. Following any sequence of trial suspension followed by resumption, the DSMB will determine whether each subsequent SAE should result in temporary suspension or whether a new stopping guideline should apply.

13 STATISTICAL ANALYSIS PLAN

Statistical methods and power analysis

The time course of the treatment responses in this Trial precludes an interim analysis. The primary aim (seizure freedom) will be assessed in months 25-36 following treatment. By the time this information is available for a meaningful number of patients recruitment will have been completed. We will monitor the outcome data with respect to adverse events and will consider stopping enrollment based on those findings (see Adverse Event Monitoring).

Specific Aim 1: Primary outcome measures of seizure response.

The primary goal of Specific Aim 1 is to demonstrate that the 3-year seizure-free rate of GKS is not inferior to that of ATL between 24 and 36 months following treatment. Although the reduction of seizures is essentially immediate for ATL and is more gradual for GK, the definition of seizure-free will be the same for both groups. Thus, a patient will be defined as seizure-free if the patient reports no complex partial seizures in the final 12 months of follow-up (months 24-36). Our experience from the Pilot Clinical Trial indicates that most patients who become seizure-free at any time following GK remain seizure-free. However, some of these patients only showed elimination of seizures at 18 months following treatment. The extension of the study to 3 years follow up will ensure that it can be determined if the improvement in the GK arm is sustained.

For the purposes of power calculations, we make several assumptions based on the range of seizure-remission rates reported for ATL and GK. The published success rates of ATL for MTLE range from ~58% (prospective, randomized trial103) to 96% 37 with the results for the subset of patients to be treated in this trial in the higher range (80-90%). We will assume that the seizure-free rate for ATL will be 80%, both as a reasonable median value and as a compromise given the multi-center, prospective, intent-to-treat design and the highly-selected, “classic” MTLE primary criterion for inclusion in the current

proposal. GK will be considered non-inferior to ATL if the one-sided 95% upper confidence bound for the difference in seizure-free rate between ATL and GK (ATL – GK) is less than 15%. This is partially based on the fact that the average seizure- free outcome for all reported patients is approximately 60%. Thus, if radiosurgery is not able to meet the accepted published standard for surgical treatment of temporal lobe epilepsy, it will be considered not to be a reasonable treatment alternative to lobectomy. If the two therapies have the same long-term seizure-free rate, 117 patients per group would have 88% power to demonstrate non-inferiority of GK. We recognize that the timing for individuals to become seizure-free will differ between the two arms. No specific hypothesis will be tested in this regard. However, point estimates and confidence intervals will be provided for the seizure-free rate and difference in seizure- free rate at each follow-up time interval. In addition time to becoming seizure-free - defined as time from the beginning of the first interval visit where a patient has no seizures to the end of the three year study - will be estimated using the method of Kaplan Meier. All patients randomized will be included in the primary analysis (intent to treat). Patients will be considered to be not seizure-free if they require any additional surgical interventions for seizure control or die during the 3- year study. Patients lost to follow-up or who drop out for other reasons will be accounted for by a multiple imputation procedure. Their assigned outcomes will be based on a logistic regression imputation model which includes treatment assignment and seizure-free status in the last assessment interval for which we have data for the patient lost to follow up. In addition a worst-case sensitivity analysis will be conducted. For that analysis subjects randomized to the open surgery arm for which the three year status is not known will be considered seizure-free and patients treated with GKS will be considered not seizure-free as this would be the "worse case scenario" with respect to demonstrating non-inferiority of GKS.

Specific Aim 2: Verbal memory comparisons

Our hypothesis is that patients treated for speech-dominant temporal lobe seizures with temporal lobectomy will show greater reduction in verbal memory than patients treated with radiosurgery. To assess verbal memory, we will use two well-validated measures from neuropsychological batteries performed at baseline and at 12, 24 and 36 months postoperatively. The long delay free recall score of the California Verbal Learning Test (CVLT-LDFR) 23 and the delayed recall score the Logical Memory subtest of the Wechsler Memory Scale – Revised (WMS-R DR) 101 provide complimentary measures of non-contextual and contextual verbal memory96. These tools were utilized in the Pilot Trial. To test the null hypothesis of equal memory performance in the ATL and GK groups, we will examine the subset of patients who undergo dominant hemisphere surgery as determined by Wada testing. Patients who are scored as “language symmetric” in the five-point lateralization scale (see Inclusion Criteria) will be excluded from this analysis (the number of such cases is expected to be very small). We will evaluate mean changes in verbal memory using a repeated measures analysis of variance model. The model will include factors for treatment, time, and patient, as well as the interaction between treatment and time. Hypotheses will be tested and parameter estimates and confidence intervals provided using appropriate contrast statements. Based on historical data we expect the CVLT-LDFR to be most sensitive to memory problems, so change in this measure will represent our primary test of the hypothesis of differential memory loss depending on treatment. However, to more fully describe the patterns of change in memory, a similar analysis will be done for the WMS-R DR. For summary purposes patients will be classified as “improved”, “unchanged”, and “impaired” on each of the measures based upon change from baseline to the 12 month assessment. While we would like to describe categorical changes at other time intervals, published data are not available to allow us to do this. These data will be presented using classifications based on relative change indices (RCIs) developed and validated in epilepsy populations We will also evaluate the patient change using the standardized regression-based Z score approach and compare the results to that using the RCI. Regression-based multiple imputation will be used to deal with missing data for those cases where patients are lost to follow-up or require additional intervention. The imputation model will include treatment and scores on all previous assessments. The analyses will be repeated that exclude subjects who did not receive the protocol-assigned treatment. For the purpose of power calculations, we assume a simplified model and our primary hypothesis are evaluated by comparing the mean change between the 2 treatment groups at 36 months. We assume that approximately 50% of patients – 58 patients per group – have dominant lobe epilepsy and will be included in this analysis. We anticipate approximately a 2.3 point difference in mean memory loss between the 2 treatment groups with a standard deviation of about 3.6, based on verbal memory change observed in a previous ATL cohort 96. Under these circumstances there would be 92% power to declare statistical significance based on a two-tailed t-test with alpha=0.05. Secondary analyses will examine changes in verbal memory among

non- dominant cases and changes in nonverbal memory and other cognitive domains among all cases, using the methods described above.

Specific Aim 3: QOL measurements

Our hypothesis is that there will be improvements in quality of life following GKS and ATL from the period between preoperative baseline and the final 36 month follow-up assessment; improvements in self-reported QOL in both groups will be greater for patients who become seizure-free, and that there will be no overall difference between patients treated with radiosurgery and temporal lobectomy by 36 months. To assess QOL, we will use the Quality of Life in Epilepsy Inventory-89 (QOLIE-89), a validated self-report measure of quality in life in patients with epilepsy 26. If model assumptions hold we will evaluate changes in QOL using a repeated measures analysis. The model will include factors for time, treatment, seizure status, baseline score and patient. Initially 3 interaction terms will also be included: time-by-treatment, treatment-by- seizure status and time-by-seizure status. Hypotheses will be tested and parameter estimates and confidence intervals provided using appropriate contrast statements. If the analyses indicate interactions are present, the data analysis will be adjusted to take into account the interaction(s). Specifically, the primary question relates to the mean change in individual QOLIE-89 overall scores from baseline to the three-year follow-up visit. Changes in QOLIE-89 scores will be evaluated for the entire sample and by patient groups defined by treatment and by seizure-free status. While we recognize that time-seizure- free has been shown to have an impact on QOL and that this factor would favor the open surgery group, we have intentionally excluded that variable from the initially planned analysis to provide a more conservative test in the QOL 3 year analysis. That term will be included in supplementary exploratory analyses. Missing data will be handled by methods similar to those described in aim 2. To estimate power we assume a simplified analysis based on results at 36 months. With a sample of 117 patients in each treatment arm as required by the primary specific aim, and if we assume that 80% of both groups will be seizure-free, this design has 90% power to detect a mean difference ≥ 55% of the standard deviation for the seizure-free vs. not seizure-free comparison at a significance level of 0.05 two-tailed. Even if there appears to be a differential impact of being seizure-free depending on treatment, requiring separate analyses by treatment group, we would be able to detect a mean difference of >75% of the standard deviation. Based on the results reported by Spencer for open surgery 91, we expect a difference of at least 10 points in QOL with an estimated standard deviation of less than 13so that we would have adequate power to detect the anticipated differences even for the within treatment analysis. The comparison between treatment groups is a test of non-inferiority. These results will be presented in the form of a one-sided confidence interval for a difference in the mean change in quality of life between the 2 groups. No specific criterion for defining non- inferiority is available. However, to provide information on the size of difference that could be detected note that if all patients are included, there is over 90% power to document that the difference is less than 40% of a standard deviation, assuming no true treatment difference. We would also plan to evaluate the difference in QOL for only those patients who are seizure-free to document that seizure-free status confers the same overall benefit regardless of how it is achieved. With 80% of patients expected to be seizure-free, there would be over 90% power to document that this difference is no greater than 45% of a standard deviation. Assume a common standard deviation of 13 – consistent with the assumption above. In that case 40% would be a difference of 5.2 and 45% would be a difference of 5.85. We will also report changes in individual QOL domains over time. For these supplementary analyses the focus will be on estimation and using graphical techniques to provide information to physicians and patients about the predicted pattern for the various quality of life measures for each of the treatments.

Specific Aim 4: Economic evaluation

Our hypothesis is that GK will be cost-effective compared to ATL. Specifically, the marginal cost-utility ratio will fall below $50,000/QALY, a threshold thought to indicate that outcomes are considered worth the cost 36. Separate cost-utility analyses will be performed for the 3-year time frame of the trial, as well as over the lifetime of the subject in order to place short-term treatment differences in perspective. The lifetime analysis will project results at the end of the trial over the lifetime of the subject, using a Markov model described below. Sensitivity analyses will pay particular attention to assumptions about stability of seizure control, costs and QOL differences over time. The analysis will adopt a societal perspective, following recommendations of the US PHS Panel on Cost- Effectiveness Analysis in Health.43, 63 Annualized costs will be assessed from the day of randomization to 3 years following treatment onset. Costs beyond the study period will be estimated from annualized costs for the 24-36

months after treatment onset, as the Multi-center cost study showed that costs did not begin to change in seizure-free patients until approximately 18 months after surgery. Health care utilization will be assessed from multiple sources. Medication (AED and non-AED) and outpatient utilization at the study site will be abstracted from the study database. Inpatient utilization at the site hospital will be calculated from inpatient billing data contained on a universal billing form (UB-04) that will be obtained on a quarterly basis. Utilization will also be tracked prospectively by subjects in modified seizure diaries. Subjects will only need to indicate the dates of care and provide a numeric code corresponding to one of 6 types of care received (e.g., outpatient visit, inpatient hospitalization, laboratory test, other test or procedure, dental care or emergency room visit). Subjects will be asked to record study site visits and hospitalizations, as well as off-site care. Diary entries will be checked against known episodes of care at the site to monitor diary compliance. The diary will also prospectively record patient and care-giver time lost from work due to symptoms or seeking care. A copy of the seizure diary is included in the Manual of Operations. Direct medical costs will be calculated from utilization data via a Medicare-based accounting-cost method used in the Multi-center cost study and described in greater detail in Appendix. Indirect costs of time that subjects and caregivers lose from work due to symptoms or seeking care will be calculated using age-adjusted, nationally-representative hourly wage rates. Utility will be expressed as quality adjusted life years (QALYs), calculated as the area under the curve (AUC) of the utility scores during each year of observation. Utility scores will be derived from the SF6D, a six- dimensional health state classification that has stronger evidence for validity and responsiveness in this population than other multi-attribute utility scales63. SF6D scores are derived from 11 items from the Medical Outcomes Study Short-Form-36 (SF-36), a generic, preference based instrument for measuring health-related QOL11, 63. All SF-36 items are included in the QOLIE-89, so no additional survey is required 11, 63. The SF6D scoring algorithm has been modified by one of us to allow direct derivation from QOLIE-89 63. CRFs have been developed for each of these evaluations and are present in the Manual of Operations. Data will be recorded manually on these forms, and then entered by the Treatment Center Study Coordinator into the on-line database. The sample size selected for the study was based on the primary goal of demonstrating equivalence in seizure-free rates between the two treatments. Because of the multiple factors affecting economic measures, it is possible that this sample size may not be sufficient to provide sufficient power to detect potentially important differences between the treatment groups for these measures. For that reason, although we plan to conduct formal hypothesis tests, the emphasis will be on estimation and a variety of summary measures/analyses will be used in an effort to fully describe the nature of the observed results and their possible economic implications. The marginal cost-utility ratio (MCUR) for the within-trial (3-year) time frame will be calculated based on the mean costs and QALYs observed in the radiosurgery (RS) and temporal lobectomy (ATL) arms, as follows: (Cost RS – Cost ATL) / (QALYS RS – QALYS ATL). The life-time MCUR will be defined in the same manner and estimated from a two-arm (ATL and RS) decision-analysis model with 8 Markov states per arm, created using commercial decision-analysis software (Data 3.5 for Healthcare, Treeage Software, Inc.). The 8 cost- and QALY-relevant states will be the state of being dead and the 7 plausible combinations of seizure status (in 1 year remission vs. not), AED status (on vs. off AEDs) and employment (employed full or part-time vs. not employed full or part-time) (There are only 7 plausible states, because it is assumed that all subjects not in remission will be on AEDs). The initial distribution among states will be the distribution observed at the end of the trial. Initial Markov state rewards will be the distributions of costs and QALYs observed over the course of the trial, using the DistSamp function within Data 3.5. Markov transition probabilities for the ATL arm will be estimated from long-term outcomes of the Multi-center Study of Epilepsy Surgery91. Long term data on seizure outcomes of radiosurgery will be estimated from a recent study that followed 15 patients and average of 6 years80. Transitional Markov state rewards will be the state-specific distributions of QALYs and costs during the third year of observation. Sensitivity analyses will be performed, using a range of assumptions about the stability of these values over time. For each MCUR, ninety-five percent confidence intervals (CI) will be produced using a method based on an angular transformation of the MCUR combined with the bootstrap 21. This method is appealing because it stabilizes the variance of the estimated MCUR even when the denominator is close to zero. The 3-year MCUR CI will be estimated with random sampling with replacement from the entire pool of patients, generating 10,000 hypothetical cohorts. The lifetime MCUR CI will be estimated using a 10,000 trial, Monte Carlo simulation within the model, during which model inputs (e.g., costs, QALYs) are sampled from the distributions observed in the trial, a process analogous to bootstrapping with replacement. The probability that each MCUR falls below an acceptability threshold of $50,000/QALY will be determined using an adoption-rule region approach and a net-benefit approach previously used in an economic trial

in Parkinson's disease.

14 CASE REPORT FORMS

Note: The ROSE Trial Case Report Forms are available in an electronic format. Printed copies of each electronic CRF can be generated by individual study sites as needed by logging into the VisionTree Optimal Care, ROSE Trial electronic database, via secured password.

Study Center _____ Patient ID#_____

Patient Initials _____

Data Requirement Checklist

	Pre-Op Baseline Screen	Treatment: TL/RS	Post Op 3 mos	Post Op 6 mo	Post Op 9 mo	Post Op 12 mo	Post Op 15 mo	Post Op 18 mo	Post Op 21 mo	Post Op 24, mo	Telephone 1, 25-26,28,29,31, 32,34, 35	Post Op 27, 30,33 mo	Post Op 36 mo
Date													
Inclusion & Exclusion Checklist	X												
Informed Consent	X												
Medical History Summary	X												
Review of Seizure Diaries	X		X	X	X	X	X	X	X	X		X	X
Focused Neuro Exam	X		X	X	X	X	X	X	X	X		X	X
Focused Post op Physical Assessment			X										
Headache and Mood	X		X	X	X	X	X	X	X	X		X	X
HVLT-R	X			X	X	X	X	X	X	X			
Review of Meds	X		X	X	X	X	X	X	X	X	X	X	X
Formal Visual Fields Exam	X									X			
Pregnancy Test	X												
Standard Scalp EEG	X									X			
Video EEG Telemetry-Scalp	X												
Neuro-Imaging MRI	X		X* (TL)			X** (RS)				X** (RS)			X** (RS)
Wada Test	X												
Neuropsych Testing	X					X				X			X
QOLIE-89	X		X			X				X			X
QOLIE-10				X	X		X	X	X			X	
Actual Life Changes in Epilepsy	X		X	X	X	X	X	X	X	X		X	X
Treatment Data		X											
Telephone Follow-up											X		
Adverse Event			X	X	X	X	X	X	X	X	X	X	X
Universal Billing - 04		X	X	X	X	X	X	X	X	X		X	X
Out Patient Billing & Coding		X	X	X	X	X	X	X	X	X		X	X
Study Withdrawal													

*** Temporal Lobectomy Arm** **** Gamma Knife Radiosurgery Arm**

15 INFORMED CONSENT

- **Consent form (Sample)**

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Radiosurgery or Open Surgery for Epilepsy (ROSE) Trial

This is a medical research study. Your study doctor(s), Paul Garcia, M.D., Nicholas Barbaro, M.D., and Patricia (Penny) Sneed, M.D. from the Departments of Neurosurgery, Neurology and Radiation Oncology will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have seizures that begin in your temporal lobe and these seizures that have not come under control using standard medications.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of radiosurgery (focused radiation, Gamma Knife Radiosurgery) with the effects, good or bad, of temporal lobectomy (standard surgical care) as a treatment for your seizures. In this study you will be treated with radiosurgery or with temporal lobectomy. You will not get both. Radiosurgery is not like what many people consider typical surgery. There are no incisions, and there is no direct entry into the body by a surgeon. Rather this is radiation given in a focused way to a specific part of the brain (in this case, where your seizures are thought to begin).

This study is financially supported by the National Institutes of Health (NIH) and several of the investigators have a part of their salary paid from these funds. Elekta Instruments (maker of the Gamma Knife) is providing funds that will be used to cover some of the clinical costs that result from complications of therapy. This disclosure is made so that you can decide if this relationship will affect your willingness to participate in this study.

How many people will take part in this study?

We expect to treat about 17 people at UCSF as our part in this study. About 234 people will take part in this study as a whole, with half receiving radiosurgery (Gamma Knife) and the other half receiving temporal lobectomy. Approximately 18 patients will participate from UCSF and the other patients will be treated at several other medical centers throughout the Unites States.

What will happen if I take part in this research study?

Before you begin the main part of the study...

You are already in the process of being evaluated for possible surgery to treat your seizures. Most of the studies listed below will already have been done as part of that routine evaluation. Your doctors and nurses will inform you about specific tests that might be done in addition to the

routine tests necessary for the routine evaluation. You will need to have the following "screening" exams, tests or procedures to find out if you can be in the main part of the study.

- You will have a physical examination, including a neurological examination similar to those done for regular medical care of your seizures.
- Your medical record will be reviewed and there will be a complete listing of all medications you use with special attention to anti-seizure medications.
- You will be asked to complete a three-month (12 week) seizure diary with documentation of at least three complex partial seizures during the diary period. The seizure diary is filled out by you at home and will be reviewed by your doctor before being used to enter you into the study.
- You will have a test of your vision (visual field examination). This is not currently a routine test for evaluation of seizures, but is necessary because one possible risk of the surgical treatment of seizures is a worsening of your peripheral vision. Because it is part of the study, there will be no charge to you or your insurance provider to have this study.
- Most patients with seizures have had a prior EEG. The information from this study will be reviewed as part of the preliminary evaluation.
- You will be admitted to the hospital for a continuous EEG recording. In order to be eligible to enter this study, your seizures must all come from one temporal lobe.
- Your MRI will be reviewed to be sure that there are specific abnormalities in the same temporal lobe where your seizures arise. Your doctor can show you these MRI changes if you haven't seen them already.
- You will have a test known as a Wada test to evaluate which side of your brain has most of your language function. This test requires you to have an angiogram (evaluation of blood vessels to the brain using a catheter placed in a groin artery and injection of a anesthetic drug into your carotid arteries. The location of language function is an important part of this study. This test is also a routine part of the evaluation of patients for routine seizure surgery.
- You will receive a complete baseline neuropsychological assessment to evaluate many aspects of memory function. These tests are routine in preparation for any type of epilepsy surgery. The following table lists the names of these studies. The results of these tests can be explained to you by your doctors if they have not already done so.

Table 1: Inclusion neuropsychological and quality of life battery

Intelligence	-Wechsler Abbreviated Scale of Intelligence (WASI)
Language	-Boston Naming Test (1983) - 60-item version -Auditory Responsive Naming Test (Hamberger et al)
Verbal Memory	-California Verbal Learning Test - Logical Memory I & II subtest from the Wechsler Memory Scale-Revised
Visual Memory	-Rey Complex Figure Test -Brief Visual Memory Test-Revised
Cognitive Processing Speed	-Trail Making Test, Parts A & B
Mood	-Beck Depression Inventory-II -Beck Anxiety Inventory
Quality of Life	-Quality of Life in Epilepsy (QOLIE-89)

During the main part of the study...

If the screening exams, tests or procedures show that you can continue to be in the study, and you choose to take part, then you will have the following tests and procedures done. You will not be randomized until you are fully informed about both procedures. Once again, you are reminded that any questions you have about the study, including about the two procedures to be used should be answered to your satisfaction before you agree to enter this study. You will also be asked to sign a form authorizing access, use, creation or disclosure of personal information about you.

- You will be "randomized" into either the radiosurgery or temporal lobectomy treatment group. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in the radiosurgery group:

- You will meet with the surgeon and radiation specialist (oncologist) who will perform this treatment in their clinics in order to have a complete explanation of the details of the treatment. This will include a discussion of the benefits and risks of the treatment (these are also described later in this document).
- On the day of your treatment (within 6 weeks of your agreeing to participate in the study) you will be brought into the hospital, and taken to a treatment area used for Gamma Knife preparation. An intravenous catheter will be placed in order to give you fluids throughout the treatment, to be able to give you small doses of medications for sedation (relaxation) should you become particularly anxious during the procedure, and to give you medications to stop a seizure if you should have one.
- A stereotaxic frame, which is a metal device used to help guide the radiation, will be placed on your head. At four places, the skin will be cleaned with antiseptic solution, local anesthetic will be injected into the skin, and four small pins will be placed into the skin in order to attach the stereotaxic frame to your skull.
- You will be taken, with the frame still on your head, to the MRI area where an MRI will be performed. In most cases, sedating medications such as Ativan will be administered through the iv catheter in order to provide sedation and reduce the chance that you will have a seizure during the MRI.
- After the MRI, you will rest while your treatment is planned on a computer and approved by your neurosurgeon and radiation oncologist. This planning process may take a couple of hours.
- You will then be taken to the Gamma Knife treatment area where radiosurgical treatment will be performed. This involves having your head attached by way of the stereotaxic frame to the Gamma Knife machine. A series of radiation doses will be administered. The entire treatment will last approximately 1-2 hours. During this time you will be in a room by yourself with a video camera monitoring you. Your blood pressure (using an automatic cuff) and oxygen saturation and heart rate (using a finger clip) will be monitored throughout the procedure. You will be able to speak to your nurses and doctors using a microphone. In most cases, you may be given additional sedating (relaxing) medication to make it easier to rest comfortably during the treatment and to reduce your chances of having a seizure during treatment. The stereotaxic frame will be removed from your head immediately after treatment, and small bandages will be placed on your skin.

- You will remain in the hospital for a short period of observation. It is very likely that you will be able to go home at the end of the day.
- You will have an MRI performed at 12 and 24 months after treatment. If the neurologist treating you has any concerns about conditions such as brain swelling, they will request additional MRIs. At 24 months after treatment you will also have a formal testing of your visual fields, such as the one you had prior to the treatment.

If you are in the temporal lobectomy group:

- You will be scheduled to see the neurosurgeon who will perform your operation in order to have a complete discussion of the details of this procedure. Just prior to your procedure, you will meet a member of the Anesthesiology Department who will explain the details of the general anesthesia required to perform the temporal lobectomy operation. Your operation will be scheduled within 6 weeks of your agreeing to participate in the study.
- You will be admitted to the hospital early in the morning on the day of your operation. The anesthesiologist who will be taking care of you will place an intravenous catheter in order to administer anesthetics and other medications during your operation. Other catheters such as an intra-arterial (blood pressure monitor) catheter, endotracheal tube ("breathing" tube), bladder catheter, will be placed after you are asleep for the operation. These will be removed at the appropriate times following surgery based on evaluation by your treating surgeon.
- You will be taken into an operating room, placed under general anesthesia and put in position for your surgery.
- Your hair will be shaved at the site of the operation and the skin will be prepared with anti-septic solution to reduce the chance of an infection.
- You will receive intravenous antibiotics to prevent infection and intravenous steroids (dexamethasone) to reduce post-operative brain swelling just prior to the start of your surgery.
- Your surgeon will perform the temporal lobectomy including a curved skin incision, opening of the bone over your temporal lobe and removal of a pre-determined portion of the temporal lobe.
- After the lobectomy is completed, the surgeon will replace your bone and fasten it in place with small metal (titanium) plates. The muscle and skin over this area will be sutured/stapled closed and a bandage will be placed.
- You will be taken to an intensive care unit for monitoring over night. This will include careful monitoring of blood pressure, breathing and neurological condition (including waking you on a regular basis to be sure that your neurological function remains normal).
- After you have reached a stable condition (usually the following morning) you will be taken to a hospital room for further post-operative care.
- Daily laboratory blood tests will be obtained until all values are appropriate for discharge from the hospital.
- When your surgeon and neurologist feel that it is time for you to be sent home, you will be discharged from the hospital (typically after 3 or 4 days).
- Your sutures/staples will be removed approximately 10 days after your surgery.
- You will have an MRI performed approximately 1 month following your surgery to look for any complications of the surgery and to see if the appropriate amount of brain tissue has been removed.

Both treatment groups:

- You will be in the study for 3 years following treatment and will be asked not to change your anti-epileptic drugs during that time unless seizures worsen and your neurologist feels that a change might help these seizures.
- After you go home, you will be asked to keep a careful diary of any seizures or auras. You will also be asked to record in the diary the times that you seek medical care, the type of care you receive and any hours of work that you or a care provider lose as a result of symptoms or seeking care.
- Because one aspect of the Trial is to determine whether one type of treatment costs significantly more than the other, you will be asked to give the Medical Center permission to release some of the information regarding cost of treatments to the investigators. Specifically, the UCSF Medical Center will provide the investigators with billing information for any inpatient hospitalizations that you have at UCSF Medical Center and for outpatient care that you receive through UCSF Epilepsy Clinic. The billing information will contain information on any diagnoses that you have, any procedures that are performed and the charges for the care that you receive at these places during the course of the trial. These data will be kept in the same way that other data will, and the investigators will make every attempt to preserve the confidentiality of this information
- You will be asked to return for evaluations by members of the UCSF Epilepsy Clinic at 3, 6, 9, 12, 15, 18, 21, 24, 30 and 36 months following treatment. At each visit you will be seen by a neurologist not directly involved in treating you who should not be told of which treatment you received. You will wear a hat to hide any surgical scars or other things that might give this away. This is being done so the doctor who is helping to count your seizures does not know which type of treatment you received. You will undergo neuropsychological testing in the Epilepsy Center (a repeat of the language and memory tests done prior to treatment) at 12, 24, and 36 months following treatment. Although no blood tests are required following treatment, you may be sent for blood tests to determine levels of antiepileptic medications, much as you already do when seeing your neurologist.

- **Study location:** All study procedures will be done at UCSF Medical Center.

- **MRI:** Based on the schedule described for each treatment group, you will have Magnetic Resonance Imaging (MRI) exams. For the MRI exam, you will lie down on a narrow bed which will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will need to lie there quietly for about one hour, during which time there will be a loud banging noise. You may feel warm during this procedure.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely. It is important to tell the study doctor if you are thinking about stopping so that your doctor can evaluate any risks from the treatment, and discuss what alternative follow-up care and testing could be most helpful for you. It is important to know that although you may stop being a subject in the study, the effects of therapies used in the study will still be presents. This is especially important if you are

in the radiosurgery group because the effects of the radiation treatment continue for at least 2 years following treatment.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

How long will I be in the study?

All patients in the study (both treatment groups) will be followed for 3 years.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to your study doctor about any side effects you experience while taking part in the study. The following details are provided as a guideline for what might happen to you during the study.

The risks and side effects related to the **radiosurgery treatment** are:

Likely

- Headaches requiring temporary (approximately 1 month) use of steroids (dexamethasone)
- MRI evidence of brain swelling
- Continued seizures until the full effect of radiosurgery takes place

Less Likely

- Surgery for removal of radiation-injured brain tissue
- Worsening of memory including verbal memory
- Changes in vision including worsening of peripheral vision or increase in “blind spots”
- Nausea or vomiting
- New seizures or uncontrolled seizures (status epilepticus)
- Depression
- Psychosis

Rare but serious

- Serious complications, including death, from seizures
- New neurological deficits such as numbness or paralysis, or loss of vision
- Delayed (several years) development of brain tumor

The risks and side effect related to **temporal lobectomy** are:

Likely

- Headaches requiring pain medication and temporary (approximately 1 month) use of steroids (dexamethasone)
- Scalp swelling lasting approximately 3 weeks

Less Likely

- Surgery for removal of radiation-injured brain tissue
- Worsening of memory including verbal memory
- Changes in visual fields (worsening of peripheral vision)
- Depression
- Psychosis

Rare but serious

- Infection requiring antibiotics or possible re-admission to the hospital for surgery
- New neurological deficits such as numbness or paralysis

For all patients in the Study the following risks are present:

- **Randomization risks:** You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.

- **MRI risks:** Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

  Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than on in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic sclerosing fibrosis (NSF). It can cause skin to tighten or scar and
can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

- **Reproductive risks:** You should not become pregnant while on this study because the drugs or other treatments that might be required to treat potential side effects (such as brain swelling) in this study can affect an unborn baby. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope *radiosurgery* will be equally effective with fewer side effects than the standard (usual) treatment, there is no proof of this yet.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting no treatment
- Getting standard treatment (lobectomy) for your condition without being in a study.
- Getting a different experimental treatment/taking part in another study.
- Gamma Knife radiosurgery is not often paid for by standard medical insurance, but his option could be explored by your treating physicians if you wish.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- UCSF's Committee on Human Research
- The National Institute of Health (NIH) including the safety committee assigned to monitor this study.
- Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

What are the costs of taking part in this study?

The costs of all visits, treatments, and tests described above will be billed to you or your insurance carrier, with the exception of visual field tests, post-treatment MRIs, post-treatment memory (psychological) tests, post-treatment Quality of Life Questionnaires which will be paid for by the study sponsor, National Institute of Health and Elekta. Insurance companies and other carriers sometimes refuse to pay the costs of treatment when individuals are participating in research. This is likely to be true if you are placed in the Radiosurgery part of the study. If this happens in your case, you will not be billed for the care your insurance will not cover. However, the cost of routine medications (seizure medications) will not be covered by the study. Financial counselors are available through the hospital accounting department to discuss this with you.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Garcia, Dr. Barbaro or Dr. Sneed, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call Dr Garcia at (415) 353-2437.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s): Dr. Barbaro at (415) 353-7500, Dr Garcia at (415) 353-2437, or Dr. Sneed at (415) 353-8900 or (415) 353-8950.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____ _____

Date Participant's Signature for Consent

_____ _____

Date Person Obtaining Consent

16 APPENDIX 1

- **Brochure (Sample)**

Radiosurgery or Open Surgery for Epilepsy

Epilepsy surgery is an alternative for some people whose seizures cannot be controlled by anticonvulsant medications.

In the past, individuals with epilepsy usually tried several anticonvulsant medications, often with poor results, for many years, even decades, before being considered for surgery. But more recently, most epilepsy specialists consider surgery sooner because studies have shown that numerous anticonvulsant medication trials, in certain individuals, are unlikely to result in the eventual complete control of epileptic seizures. Although recommendations vary, many seizure specialists now recommend that surgery be considered in patients whose seizures continue after the use of at least 2 anticonvulsant medications. These patients are considered to have "medically refractory epilepsy": seizures that continue despite the best attempts at medical treatment.

Medically refractory epilepsy can be divided into two types. *Generalized epilepsies* are conditions in which the seizures arise from the whole brain. *Partial epilepsies* present with seizures that arise from a discrete area in the brain, sometimes referred to as the "epileptic focus", a "hot spot" that is considered the source of seizures. Patients with partial epilepsies are usually good candidates for epilepsy surgery.

In order to be considered for epilepsy surgery, a pre-surgical evaluation is necessary and consists of several studies that are designed to:

- **confirm the diagnosis of epilepsy**
- **determine if the seizures are partial and well localized in onset**
- **determine if the seizure "hot spot" is in an area that can be safely removed**

The traditional method of epilepsy surgery is *open surgery* in which the neurosurgeon performs a craniotomy, consisting of removal and replacement of a "window" of skull to expose the underlying brain and removal of the seizure focus. This operation requires a general anesthesia and several day stay in the hospital for recovery. For many patients this is the only option other than continuing to try additional medications.

***Radiosurgery* is a minimally-invasive radiation procedure used to treat tumors and other abnormalities of the brain, and is currently being investigated as an**

alternative to open surgery treatment alternative for a very select group of patients with medically refractory partial epilepsy. The Gamma Knife® radiosurgery instrument used in this study uses tightly focused beams of radiation to injure the surgical target, rather than removing it with open surgery. Gamma Knife radiosurgery does not require an inpatient hospital stay.

UCSF Patient Brochure

July 25, 2009

Currently, there is a trial sponsored by the National Institutes of Health and Elekta, the company that manufactures the Gamma Knife, that is designed to compare advantages and disadvantages of open surgery versus radiosurgery. The ROSE Trial (Radiosurgery or Open Surgery for Epilepsy) is being conducted in major epilepsy centers across the US and Canada.

For more information about this trial:

- **ask your neurologist or epileptologist**
- **http://www.clinicaltrials.gov/ct2/show/NCT00860145?term=radiosurgery+and+epilepsy&rank=1**
- **http://neurosurgery.ucsf.edu/index.php/clinical_trials_epilepsy.html**

Appendix 2: Guidelines for Determination of Competency of Consent for Surgical Trials.

Examples of formal competency assessment that are suggested, but not required for use in the capacity evaluation include the MacArthur Competence Assessment Tool – Clinical Research (MacCAT-CR) and the Assessment of Consent Capacity—Randomized Clinical Trials (ACC-RCT). Alternatively, sites may use procedures approved by their local IRB for determination of competency of consent for surgical trials. An example of one procedure approved by a local IRB is outlined below.

Below is the IRB Criteria for Consent used at the University of Virginia for consideration in participation in epilepsy treatment trials.

Criteria for Consent Process

Rationale:

The individual who is responsible for determining whether a prospective subject has the capacity to consent must have appropriate expertise necessary to make such a determination (board-certified neurologist).

The determination for consent may rely on individual observation of and interaction with the potential subject. In general, an assessment an individual's capacity to consent should be based on her/his:

• Ability to communicate a choice;
• Ability to understand relevant information;
• Ability to appreciate the nature of the situation and its likely consequences; and,
• Ability to manipulate information rationally (1)

Questions appropriate to assess these capabilities include:

• Can you tell me what will happen if you agree to take part in this study?
• How might this study help you?
• How might this study not help you, or even hurt you?
• Do you have to be in this study?
• What would you do if you wanted to leave the study?
• What will happen if you decide not to be in the study?

Similarly, an individual may be considered unable to provide consent if he or she has:

• An inability to express or communicate a preference or choice
• An inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (does not understand that he/she may be hurt or may not be helped or can not distinguish research from treatment); and/or,
• An inability to provide a logical rationale for participation/no participation in a study (cannot address risk/benefit-related reasons for or against participation in a study

Planning a built-in waiting period, such as allowing the cognitively impaired patients to take the informed consent home with them, within the consent process will allow potential participants time to consult with family members about whether or not to participate. In the epilepsy patient population, there are individuals who are cognitively impaired due to static encephalopathy; however, they live on their own and are capable of consenting to their own care. Therefore, the

study is not seeking surrogate consent; rather we intend on extending the consenting period for those patients to allow for consultation and discussion with family members or trusted others.

Capacity to Consent Checklist:

The following steps will be taken to determine the capacity of a potential subject to give consent for themselves.

A. If there is concern that a potential subject/ subject may be cognitively impaired a determination of incompetence will be made after an evaluation by a person with the appropriate expertise to make such a determination as delegated by the PI. If the subject is a patient in the UVa Medical Center, the Medical Center Policy No. 0024 will also be followed. The determination of competency must be documented in writing.

B. The following methods below will be used to determine capacity for consent:

Check any applicable methods to be used.

_X___ Subject is also a patient in the UVa Medical Center and Medical Center Policy No. 0024 will be followed.

___X_ Will rely on individual observation of and interaction with the potential subject as well as the opinion of the medical provider or caregiver, when available. The prospective subject should demonstrate competence in relation to the proposed study in order to be judged capable of providing informed consent for that study. In general, an assessment an individual's capacity to consent will be based on her/his:

• Ability to communicate a choice;
• Ability to understand relevant information;
• Ability to appreciate the nature of the situation and its likely consequences; and,
• Ability to manipulate information rationally (1)

_X____The individual's abilities will be assessed by discussing the proposed study with her/him and then asking specific questions. Such questions may include:

• Can you tell me what will happen if you agree to take part in this study?
• How might this study help you?
• How might this study not help you, or even hurt you?
• Do you have to be in this study?
• What would you do if you wanted to leave the study?
• What will happen if you decide not to be in the study?

C. An individual will be considered unable to provide consent if he or she has:

• An inability to express or communicate a preference or choice (cannot make up his/her mind, is comatose, or has severe psychotic thought disorders, etc.);
• An inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (does not understand that he/she may be hurt or may not be helped or cannot distinguish research from treatment); and/or,
• An inability to provide a logical rationale for participation/no participation in a study (cannot address risk/benefit-related reasons for or against participation in a study.

3. The following steps will be taken to document the determination of competency to consent.

A note to file will be written and filed in the study files and/or medical records to describe the consenting process. The note will include a description of methods used to determine capacity of the subject to consent. The note should also include the name of the person determining competency of the subject. May use the SOM CTO form Determination of Capacity to Consent.

4. When will subjects capacity to consent be assessed?

Prior to initial consenting process if there is a concern that the potential subject has a cognitive impairment.