A Phase II Study

Phase II Trial of Seizure Prophylaxis in Brain Tumor Patients Undergoing Neurosurgical Procedure

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2 LIST OF ABBREVIATIONS

AE	Adverse Events
AED	Anti-Epileptic Drug
ALK	Alkaline Phosphatase
ATRX	Alpha-Thalassemia/mental Retardation syndrome X-linked gene
BID	Twice a Day (from Latin *bis in die*)
$[Ca^{2+}]_I$	Intracellular calcium
CAP	College of American Pathologists
CBC	Complete Blood Count
CBZ	Carbamazepine
CICR	Calcium-induced calcium release
CLIA	Clinical Laboratory Improvement Act
CNS	Central Nervous System
COLA	Commission on Office Laboratory Accreditation
CrCL	Creatinine Clearance
CPC	Cancer Protocol Committee
CRF	Case Report Form (eCRF is for electronic CRF)
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochromes P450
DCI	Duke Cancer Institute
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DUHS	Duke University Health Systems
DUMC	Duke University Medical Center
EIAED	Enzyme Inducing AED
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
FDA	US Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GTC	General tonic-clonic
GTR	Gross Total Resection
HGG	High Grade Glioma
HRPP	Human Research Protection Program
HRQOL	Healthcare related quality of life
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
ILAE	International League Against Epilepsy
IP3	Inositol 1,4,5-triphosphate
IRB	Institutional Review Board
IT	Information Technology
IV	Intravenouss
KPS	Karnofsky Performance Score
LCM	Lacosamide
LGG	Low Grade Glioma
LEV	Levetiracetam
LTG	Lamotrigine
MGMT	O-6 Methylguanine-DNA Methyl Transferase
MSR	Maximum Safe Resection (gross-total, sub-total, biopsy)
NS-CRU	Neurosurgery-Clinical Research Unit
OARC	Office of Audit, Risk and Compliance
PBT	Phenobarbital

PHT	Phenytoin
PI	Primary InvestigatorQAP Quality Assurance Program
QID	Four times each Day (from Latin *quater in die*)
QOL	Quality of Life
QOLIE	QOL in Epilepsy
RCA	Research Compliance Assurance
REDCap	Research Electronic Data Capture™
RIO	Research Integrity Office
RDSP	Research Data Security Plan
RyR	Ryanodine
SAE	Serious Adverse Effect
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SOCOMM	Safety Oversight Committee
SOPs	Standing Operating Procedures
STR	Sub-total resection
POS	Partial Onset Seizures
ULN	Upper Limit of Normal
WHO	World Health Organization
VPA	Valproic Acid

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

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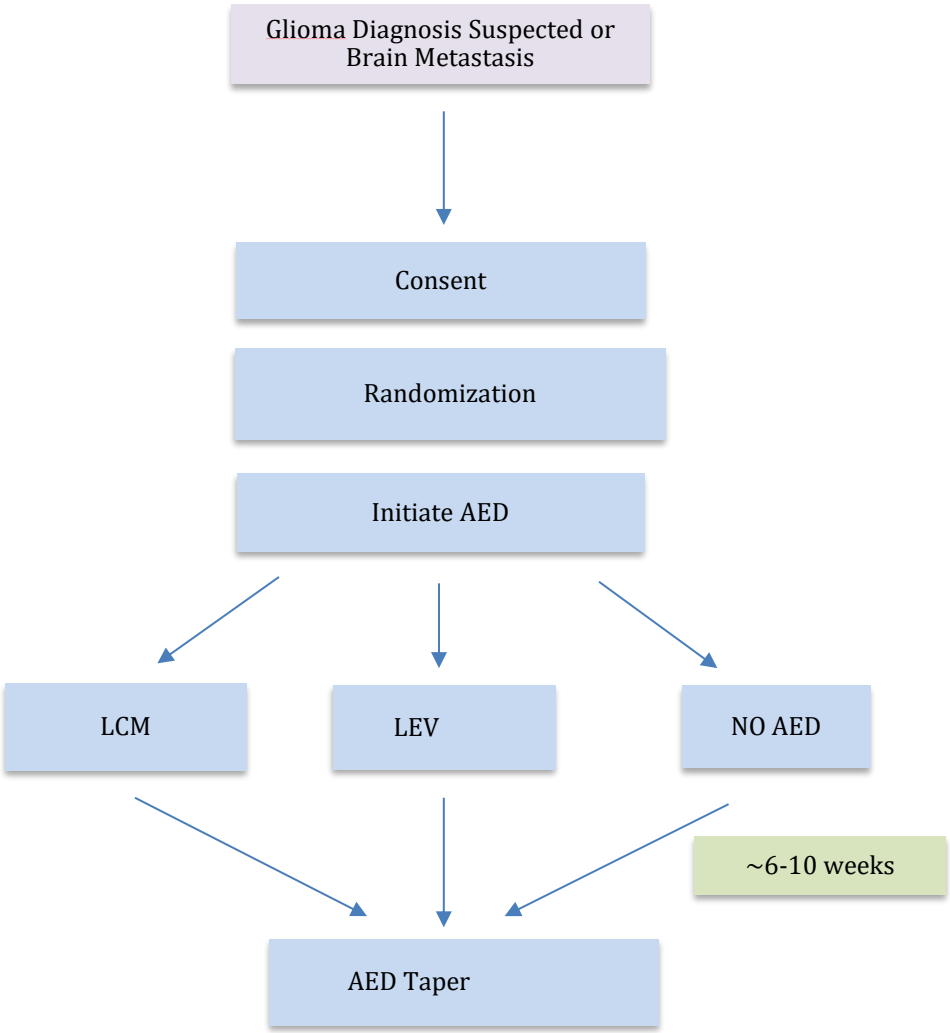
4 STUDY SCHEMA



5 BACKGROUND AND SIGNIFICANCE

5.1 Study Disease

Seizures are a debilitating complication of brain tumors. Aberrant and repetitive neuronal firing leads to the generation of seizures. Approximately 75% of patients with low grade tumors and 25% with high grade tumors suffer from seizures compared to 0.5-1% of the general population [2]. Slower growing, low grade tumors are associated with higher epileptogenicity, while faster growing, high grade tumors are associated with seizures secondary to mass effect [3]. Higher seizure frequency has been associated with reduced cognitive function and Health-Related Quality of Life (HRQOL) and strips patients of driving privileges for 6 months on average in the US, thus affecting daily functional activities of living [4]. While surgery can be potentially curative of tumor-related seizures by resecting the nidus of seizure activity, it could also cause seizures due to irritation of the cortex, hemorrhage at the surgical site, and cerebral hypoxia and acidosis during surgery [5].

The current guidelines recommend against peri-operative seizure prophylaxis in patients who have never had a seizure, and to taper Anti-Epileptic Drug (AED) therapy after the first post-procedure week [6,7]. However, these guidelines were based on older generation AEDs [(Phenytoin (PHT), Phenobarbitol (PBT), and Valproic Acid (VPA)] that were associated with significant side effects and drug-drug interactions. Since these guidelines were published in 2000, and reaffirmed in 2003 and 2008, newer generation AEDs have emerged with more favorable side effect profiles [8]. LCM, a third generation AED and LEV, a second generation AED, are both well tolerated with unique mechanisms of action.

Given the reduced risk of adverse event occurrence with newer AEDs, the clinical use of AEDs as prophylaxis has increased [9]; however, there have been no updated guidelines and there is a lack of clinical trial data to reflect this practice. LCM is US Food and Drug Administration (FDA) approved as adjunctive and monotherapy for partial-onset seizures and LEV is approved as adjunctive therapy [10 11]. Their promising roles in brain tumor patients continue to be explored.

5.2 Study Agents

5.2.1 Mechanism of action

Lacosamide: LCM is a sodium channel blocker, enhancing slow inactivation, which is unique. Other sodium channel blocker AEDs enhance fast sodium channel inactivation [12]. The activation state of voltage-gated sodium channels in the cells determines the potential for neuronal excitability [12]. Sodium channels can either be in the resting, fast inactivated, or slow inactivated state (Figure 1A). In the resting state, the sodium channels are closed and can be opened by the depolarization of the membrane potential and therefore lead to neuronal activity [13]. Shortly after depolarization, the sodium channels shift into the fast inactivated state; they close their channels from inside the neuron and are unable to be activated [13]. Older generation AEDs work by prolonging this state (CBZ, PHT, and LTG) [13]. After the fast inactivated state, sodium channels return to their resting state [13]. However, in conditions of prolonged depolarization and repetitive neuronal stimulation, the sodium channels can assume a slow inactivated state by closing the pore inside the channel [13]. LCM works by enhancing this effect [13]. In doing so, LCM stabilizes hyperexcitable neuronal membranes that are most associated with seizures [13]. At the same time, it does not affect the ability to recover from slow inactivation; thus, it inhibits neuronal firing and reduces long-term sodium channel availability without affecting physiological function [13]. Chemically, it is a member of a series of functionalized amino acids [13]. Its chemical structure is $C_{13}H_{18}N_2O_3$ and its active drug substance is (R)-2-acetamido-*N*-benzyl-3-methoxyproprionamide (Figure 1B) [13].

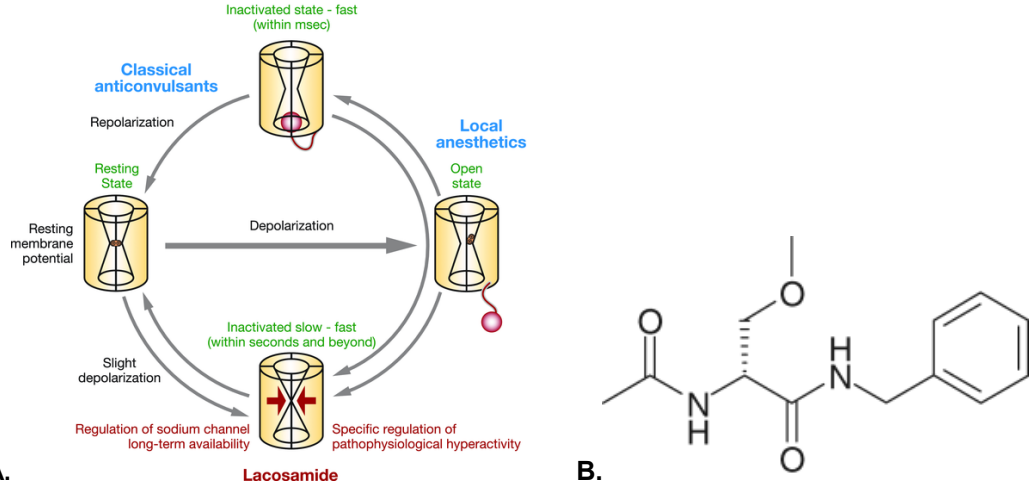


Figure 1. A. Voltage-gated sodium channels and the role of LCM [14].
B. Chemical structure of lacosamide (C13H18N2O3)[14]

Levetiracetam. LEV's anti-epileptic properties have been widely studied, but a single mechanism has yet to be elucidated. Its primary mechanism of action is binding to the synaptic vesicle protein SV2A, an essential

presynaptic membrane protein in neuronal transmission that is expressed ubiquitously in the brain [15]. By doing so, LEV decreases neurotransmitter release in states of epileptiform burst firing [16].

LEV also inhibits calcium release from intraneuronal stores and high voltage activity (N-type) calcium channels [11]. In regards to intraneuronal stores, LEV has been shown to inhibit the Inositol 1,4,5-triphosphate (IP3) and Ryanodine (RyR) receptors, two major receptors involved in calcium-induced calcium release (CICR), which effectively decreases intracellular calcium ($[Ca^{2+}]_i$) [17]. Ca^{2+} is part of important second messenger systems associated with neurotoxicity and neuronal plasticity [17]. Elevations in ($[Ca^{2+}]_i$) and alterations in calcium homeostatic mechanisms have been implicated in acquired epilepsy resulting from injury [17]. Thus, LEV's effect on calcium plays a part in its anti-epileptic ability.

LEV's impact on GABAergic (transmitting or secreting gamma-aminobutyric acid) mechanisms has been both favored and rejected, with discoveries only applicable or studied in specific diseases, such as those related to mesial temporal lobe epilepsy and not necessarily tumor related epilepsy [18,19].

Lastly, LEV has also been suggested to inhibit O-6 methylguanine-DNA methyltransferase (MGMT) [20]. While not directly related to its anti-epileptic effect, it is relevant in this population, since MGMT is a Deoxyribonucleic Acid (DNA) repair protein that plays a role in resistance of gliomas to alkylating agents [20]. Inhibiting MGMT thus inhibits malignant glioma cell proliferation, and increases sensitivity of gliomas to temozolomide, first-line chemotherapy for malignant gliomas [20].

LEV's chemical formula is $C_8H_{14}N_2O_2$ [15]. It is the S-enantiomer of a-ethyl-2-oxo-1-pyrrolidine acetamide [15].

5.2.2 Pharmacokinetics

Lacosamide. LCM's time to peak is 1-4 hours and the half-life is 13 hours, allowing for twice daily dosing [21]. LCM achieves steady-state concentrations after 3 days of BID dosing [14]. It has negligible protein binding [14]. Therapeutic drug monitoring is not routine given its predictable pharmacokinetics, except in instances of liver and/or kidney failure or to evaluate drug compliance [22]. Its absorption is not affected by food intake [23].

Levetiracetam. LEV's time to peak is 0.5-1 hour and the half-life is 6-8 hours [15,24]. It achieves steady-state concentrations after 48 hours of BID dosing [25]. LEV does not require routine drug monitoring for therapeutic levels because of its predictable pharmacokinetic profile and wide therapeutic margin [11,15]. It has negligible protein binding [26]. Its absorption is not affected by food intake [15].

LCM and LEV are both renally cleared [27]. Approximately 40% of LCM is excreted unchanged, 60% as an inactive metabolite formed by the liver (via several Cytochromes P450 (CYPP450) and CYP-independent mechanisms, mainly cytochrome CYP2C19), and the remainder as a polar fraction thought to be serine derivatives [10,28]. Nearly 100% of LEV is excreted by the kidneys, approximately 66% unchanged and the rest as a metabolite formed by hydrolysis in the blood [29,30].

5.2.3 Formula dosing

Lacosamide. LCM is available in IV, oral liquid and oral tablet formulations and has near 100% oral bioavailability [21]. It is dosed twice a day with a usual starting dose of 50mg BID for adjunctive therapy or 100mg BID as monotherapy [10,21]. It can alternatively be initiated with a single loading dose of 200mg, followed by a maintenance dose regimen of 100mg BID approximately 12 hours later [10]. The maintenance dose can be titrated 50mg BID over a week to a maximum dose of 400mg/day [21,31]. Discontinuation of LCM should be done gradually with a weekly taper of approximately 200mg a week [10].

No dose adjustment of LCM is necessary in mild to moderately renally impaired patients; however, in patients who have creatinine clearance (CrCl) <30 ml/min and are diagnosed with end stage renal disease (ESRD), the maximum recommended dose is 300mg/day [32]. The maximum recommended dose for patients with mild to moderate hepatic impairment is 300mg/day, mainly attributed to associated renal dysfunction in patients with

moderate hepatic impairment [10]. LCM has not been systematically studied in patients with severe hepatic impairment, and is thus not recommended for these patients [23].

Levetiracetam. LEV is available in IV, oral liquid and oral tablet formulations, including extended release [15]. It has near 100% oral bioavailability. It does not require slow titration during initiation of therapy [25]. LEV is usually dosed twice a day, unless it is the extended-release form, which is once a day. The usual starting dose is 500-1000mg BID, with a maximum dose up to 3000mg/day [15]. Discontinuation of LEV should be done gradually as prescribed by the primary physician.

LEV must be renally adjusted for patients with CrCl less than or equal to 80 ml/min/1.73m^2 [33]. It does not need to be adjusted for mild-to-moderate liver impairment, but it does need to be reduced for severe liver impairment, mainly because often patients with severe liver dysfunction also have some renal impairment [34].

5.2.4 Drug-drug interactions

Drug-drug interactions are relevant in patients with brain tumors, who take concomitant medications such as dexamethasone and chemotherapies that are metabolized via the CYP450 system. Older generation AEDS that are enzyme-inducing AEDs (EIAEDs) increase clearance of chemotherapy and dexamethasone, reducing efficacy, while other AEDs that are enzyme inhibitors potentially increase the toxicity of chemotherapies [35,36]. In addition, AEDs themselves can build to toxic levels due to the drug-drug interactions, requiring more therapeutic monitoring of AED levels in these older generation drugs [35]. Such issues are alleviated with LCM and LEV.

LCM has low potential for pharmacokinetic drug-drug interactions due to its low protein binding, which minimizes potential displacement of other drugs and because it does not inhibit or induce any of the CYP isoenzymes in a clinically relevant manner [23,37,38]. LEV also has no known significant pharmacokinetic interactions since it is not metabolized through the liver [13,27].

5.2.5 Adverse Events

Lacosamide. LCM's most common adverse events (AEs) based on phase IIB/III trials in partial-onset seizures were related to central nervous system (CNS) and gastrointestinal effects [39,40]. Dizziness, headache, nausea and diplopia were the most common in a pooled analyses of the trials, occurring at ≥10% in all doses combined (200-600mg/day, N=944) [41]. Other less common AEs included nystagmus, ataxia, vomiting, fatigue, somnolence, and headache [39 40,42]. Incidence appeared dose related, more apparent during the initial titration phase, and less frequent during the maintenance phase [14]. The most common AEs that led to discontinuation of the drug were dizziness and abnormal coordination, and these occurred at the higher dose of 600mg/day [42]. There were no serious safety concerns regarding hematologic or clinical chemistry values identified [42]. Moreover, another meta-analysis of 10 randomized controlled trials of LCM for various indications determined LCM was not associated with any apparent adverse effect on cognition [43].

Levetiracetam. LEV is well tolerated; however, it can cause behavioral AEs such as aggression, irritability, and anger, as well as somnolence and cognitive side effects. Behavioral AEs reportedly occur in approximately 13% of patients, but up to 30% for some AEs such as irritability or anxiety [44]. It has been associated with suicidal tendency and has a contraindication for use in patients with past history of psychiatric illness [45].

5.2.6 Efficacy in Epilepsy

Lacosamide. LCM was FDA approved as adjunctive therapy and monotherapy for partial-onset seizures (POS) in adults in 2008 and 2014, respectively [10].

LCM is well known to be effective and well tolerated as an adjunctive agent for drug-resistant partial epilepsy, especially when combined with a non-sodium channel drug [46]. This has been demonstrated in at least three

randomized controlled trials, as well as other studies [21]. More relevant to this study, it was more safe and efficacious to add LCM in patients who had breakthrough seizures on low dose LEV (<1500mg/day) than to increase the dose of LEV and thus increase the risk of behavioral side effects [47].

Studies have been very supportive of LCM's efficacy and safety as monotherapy in POS. A retrospective review of 66 patients across 6 centers with POS treated with LCM monotherapy revealed that 63.6% (42/66) remained seizure-free during follow up (up to 54 months) [48]. The patients were grouped into those who had LCM as first line therapy (n=18) and those who had previously been treated with an AED (n=48). No difference in efficacy between the two groups in terms of outcomes or tolerability was found. Only 3/66 (4.5%) of patients had to discontinue therapy due to side effects, which were generally mild [48]. Another study prospectively followed patients who were converted to LCM monotherapy after 1-year seizure freedom on LCM add-on therapy, followed by withdrawal of the concomitant AED [49]. 55.2% (32/58) patients were seizure free at one year from withdrawal of the background AED, with those who were on more than three lifetime AEDs more likely to have a seizure [49]. Side effects were mild to moderate in 20% (12/58) of patients [49]. This study was performed on patients with POS with or without generalization [49]. Other studies, including double-blind studies, have also supported the effectiveness and safety of conversion to LCM monotherapy after withdrawal of background AEDs [50].

In terms of generalized epilepsy, there have been studies to demonstrate LCM therapy being effective in these patients [51], and studies are still ongoing to verify this (NCT01969851, NCT02408549).

Levetiracetam. LEV was FDA approved in 1999 as adjunctive therapy for POS in adults with refractory generalized myoclonic seizures [11]. Since then, LEV is widely used for POS, general tonic-clonic (GTC) seizures, and generalized myoclonic seizures based on studies demonstrating its efficacy as adjunctive and monotherapy in these patients [39,52-60]. The 2013 International League Against Epilepsy (ILAE) updated review on epilepsy stated that LEV has level A evidence as a monotherapy for POS in adults and Level D evidence as a monotherapy for newly diagnosed or untreated GTCs [61]. This was based on trials showing non-inferiority compared to carbamezapine (CBZ), the prior first line therapy for POS [57].

A recent prospective, open-label, randomized study further supported LEV monotherapy as non-inferior to CBZ in POS, resulting in 71 vs. 78% seizure freedom at 6 months (p=0.253). They were both well tolerated, but LEV had a better overall quality of life (QOL), measured by the QOL in Epilepsy (QOLIE)-10 questionnaire. However, LEV was associated with more behavioral changes, such as aggression and anxiety [45,57,62].

5.2.7 Efficacy in Brain Tumors

Seizures associated with brain tumors belong to the category of POS, either with or without secondary generalization [63]. Since it is relatively new, there is limited data on LCM in brain tumors. Current data supports its tolerability and efficacy as an add-on agent [64]. One retrospective analysis of 70 patients with primary brain tumors reported a decrease in seizure frequency in 66% (47/70) of patients [65]. There are currently ongoing randomized, double-blind, placebo-controlled trials of LCM for seizure prophylaxis in patients with high grade gliomas (NCT01432171), and one as adjunctive therapy to refractory epilepsy in patients with low grade glioma (LGG) (NCT02276053). Its related side effects are the same as in non-brain tumor patients, mainly dizziness at high doses [65].

LEV, on the other hand, has evidence to support its use as a first line agent in brain tumors, due to its efficacy, low drug-drug interactions, and tolerability [66-68]. Seizure freedom with LEV has ranged from 76-91% with seizure reduction by half in 100% of patients [3,67-69]. Recent studies have also shown it has a potential anti-tumor effect as an added benefit secondary to its role as an MGMT inhibitor, although this role has been contested with later analyses and is still being studied (NCT02815410) [20]. Its risk of emotional instability (aggression, depression or irritability) is about the same 5-13% risk as in non-brain tumor patients, with a reported 0.4% incidence of psychosis 4 weeks after initiating LEV [67,69].

5.2.8 Clinical Experience

In our institution's experience, peri-operative LEV prophylaxis at a dose of 500mg BID was well tolerated among patients, with a 10% rate of AEs, mainly irritability, agitation and fatigue. At that dose, there was not a statistically significant reduction in post-operative seizure rates (34.6% seizure rate at this dose of LEV) among patients with newly-diagnosed high-grade gliomas (Pro00047350 Descriptive and Cost Analysis of Post-Operative Anti-Epileptic Drugs in Malignant Glioma). However, subsequent to the year studied, patients were initiated on 1000mg BID.

The goal of this study is to evaluate the impact of LCM, LEV or no AED on the re-admission rate and number of emergency room visits in the post-procedure period. If the use of an AED is shown to be beneficial, it is possible that LCM could be a preferable alternative for some patients, especially for those who do not tolerate LEV due to the behavioral side effects.

5.2.9 Study Purpose and Rationale

The primary purpose of this study is to evaluate 30-day readmission rates and ED visits through randomizing subjects to "no AED" or to the 2 primary AEDs used in this patient population here at DUMC.

Current guidelines recommend against peri-operative seizure prophylaxis for patients with newly diagnosed brain tumors; however, they were based on older generation AEDs that were associated with severe toxicities and drug-drug interactions. In light of newer generation AEDs with more tolerable safety profiles, some neurosurgeons and neuro-oncologists prescribe AEDs to patients for prolonged periods of time after surgery, despite these guidelines; this has also been the practice here at DUMC. Given the lack of recommendation for AED prophylaxis in the peri-operative period by the neurosurgical guidelines, which is contrary to Duke's practice, and given the cost and potential side effects of AEDs, it was determined that it is now time to formally assess the impact and side effect profile of the use or not of AEDs. I If determined that AED is necessary, this study will also attempt to evaluate the side effect profile of the commonly used AED at Duke (levetiracetam) versus a newer AED (lacosamide).

The question most relevant to Duke neurosurgeons is the rate of readmission and ED visits after a Maximum Safe Resection (MSR) (gross-total, sub-total or biopsy), a measurable patient outcome to their surgery. If there is benefit on these rates from having an AED, that would provide support for neurosurgeons to prescribe AEDs. If there is no difference in readmission rates/ED visits between those who did and did not receive an AED, then there would be much more support against AED prophylaxis. If the adverse side effects of the AEDs studied are significant, then there will be a greater consideration of risk to benefit.

The risks of seizures in the perioperative period are very small, which is supported by the current guidelines recommending against seizure prophylaxis in the peri-operative period and further demonstrated by the incidence of peri-operative seizure of 34.6% observed in the Duke retrospective review (Pro00047350 Descriptive and Cost Analysis of Post-Operative Anti-Epileptic Drugs in Malignant Glioma). Thus, variables related to seizure incidence from use of AEDs all are important to study, but written as exploratory variables in this protocol. The data from this latter analysis may be suggestive of the impact of AED prophylaxis on seizure outcomes, but it is unclear at this point how significant the outcomes will be based on our knowledge of seizure rates. The outcome of this study may, therefore, impact Duke practice.

Overall, given the paucity of studies in the literature evaluating this question, it would have a significant contribution to outstanding literature and implications for standards in general, although the goal of this protocol is not to modify or update the general standard.

The benefit of a prospective, randomized study is to remove the bias that occurs in an observational study because the latter allows neurosurgeons to let their own practice/biases decide whether a patient should receive AED treatment and which type.

LEV and LCM are newer generation AEDs with better safety and tolerability than first generation AEDs, and studies lean towards their effectiveness in patients with POS, which affect a great deal of patients with primary brain tumors. LEV, a second generation AED, has been often used in these patients, but its side effects of irritability, somnolence, and rarely, psychosis, may be limiting for these patients already affected by cognitive and behavioral issues as a result of their tumors. LCM is a third generation FDA-approved AED for POS, and initial studies have shown its effectiveness as monotherapy after patients have failed and been weaned off other AEDs. Its safety and tolerability has been demonstrated in brain tumor patients, but studies evaluating the efficacy of LCM in this population are still lacking.

In this protocol, we will assess optimal seizure prophylaxis management during the post-procedure period for patients undergoing MSR for suspected diagnosis of new, recurrent, or transformed glioma (WHO grade I-IV) or brain metastasis. This will be determined by observing the impact of LCM, LEV, or no AED on whether visits to the emergency department (ED) or hospital re-admissions occur within 30 days after MSR. A secondary endpoint will evaluate the safety and tolerability of LCM and LEV. Exploratory endpoints will evaluate admission duration for theMSR, number of post-procedure provider communications (telephone, email, and additional clinic encounters, etc.), and patient risk factors associated with post-procedure seizure.

6 OBJECTIVES AND ENDPOINTS

Table 1: Objectives and Endpoints

	Objective	Endpoint	Analysis
Primary	Assess the impact of LCM, LEV or no AED in patients with suspected glioma (WHO Gr I-IV) or brain metastasis on ED visits and readmissions within 30 days of MSR	Percentage of patients with an ED visit or hospital readmission within 30 days of MSR	See Section 13.4
Secondary	Assess the safety and tolerability profile of LCM and LEV	Percentage of patients who experience an adverse event of special interest within the first 30 days after MSR	See Section 13.5
Exploratory	Describe the duration of admission stays among patients treated prophylactically with LCM, LEV, or no AED	Median duration of initial admission stay for MSR	See Section 13.6.1
Exploratory	Describe the number of provider communications (email, telephone, or additional clinical visits) among patients treated prophylactically with LCM, LEV, or no AED	Frequency distribution for the number of provider communications (email, telephone, or additional clinical visits) that occurred within 30 days of MSR.	See Section 13.6.2
Exploratory	Describe the usage of intraoperative AED	Percentage of patients requiring intraoperative AED	See Section 13.6.3
Exploratory	Assess the impact of LCM, LEV, or no AED on post-procedure seizure occurrence	Percentage of patients experiencing post-procedure seizures during the 30-day post-operative phase.	See Section 13.6.4
Exploratory	Describe the frequency of changes in AED dosage, type of AED, addition or discontinuation of AED	The frequency of changes in dosages, type of AED, addition or discontinuation of AED that occur within 30 days of MSR	See Section 13.6.5
Exploratory	Evaluate patient risk factors for post-procedure seizure	Statistically significant association of specific risk factors with rate of post-procedure seizure during the 30-day post-procedure phase	See Section 13.5.6

7 INVESTIGATIONAL PLAN

7.1 Study Design

The protocol will assess the need for AED prophylaxis during the post-procedure period in patients undergoing MSR for a suspected diagnosis of glioma (WHO grade I-IV) or brain metastasis. Patients (n=232) will be consented and randomized at their pre-operative assessment, either at their pre-operative clinic visit or in the ED, if that is the time of their initial presentation prior to surgery. There will be three arms to the study – patients will be randomized to LCM, LEV, or control (no AED). Randomization will be stratified by suspected grade (LGG vs HGG). The AED can be initiated anytime within 48 hours before a MSR incision.

Patients already on AEDs specifically to treat seizures will be excluded. Those patients taking AEDs for any diagnosis other than seizures will be included (e.g. Gabapentin for neuropathic pain, Topiramate for migraine, benzodiazepines as sleeping aid, etc).

Patients taking AEDs for seizure prophylaxis and without clear history of seizures will be included. If already on LEV and randomized to LCM and vice versa, patient will be cross-taper, a week prior to surgery, as follows:

- If on LCM 100mg BID and need to taper to LEV:
- Start LEV, reduce LCM to 100/50 x 2 days, then 50/50 x 2 days, then 50 daily x 2 days, then off

- If on LCM and need to taper off:
- Reduce LCM to 100/50 x 3 days, then 50/50 x 3 days, then 50 daily x 3 days, then off

- If on LEV and switch to LCM:
- Start LCM, reduce LEV to 1000/500mg x2 days, 500/500mg x 2 days, 500 daily x 2 days, then off

- If on LEV and need to taper off:
- Reduce LEV to 1000/500 x 3 days, then 500/500 x 3 days, then 500 daily x 2 days, then off

Patients consented less than a week prior to surgery, who were on LCM and get randomized to LEV (or vice versa), will start the new medication, cut their current regimen by half, and stop the day of surgery.

Doses will be either LCM 100mg twice a day (BID) (Arm A), LEV 1000mg BID (Arm B), or no AED (Arm C). If a patient is randomized to Arm C and undergoes tumor mapping, the patient is allowed to receive one dose of AED in the operating room. If a patient is randomized to Arm A or Arm B and takes the morning dose of their AED, they do not need an intra-operative dose of AED. If a patient has a seizure during the post-procedure period, AEDs will be adjusted at the discretion of the treating physician. However, if a patient has intolerable side effects, patients will be changed to a different dose of the same medicine before consideration of another AED [i.e., BID to four times a day (QID) dosing if patient experiences diplopia on LCM].

Patients with high-grade tumors (newly-diagnosed or transformed) will be treated with standard radiation and temozolomide therapy per the Stupp protocol [25,70]. For these patients, an AED taper will be initiated at the first clinic visit after completion of radiation. For patients with a low-grade tumor or recurrent disease of any grade, an AED taper will be initiated at the first scheduled post-procedure visit, approximately 6-10 weeks after the operation. LCM will be tapered by 100mg a week one week at a time. LEV will be tapered 500-1000mg one week at a time.

7.1.1 AED initiation

At study enrollment, patients will be randomized to either LCM, LEV or no AED. Enrollment can occur at the pre-operative visit before MSRor in the emergency room at the time of patient's first presentation. AED can be initiated anytime within 48 hours of the first MSR incision.

7.1.2 AED titration

If a patient experiences seizure during the follow up period, AED doses will be modified per treating physician preferences.

7.1.3 Post-procedure data collection

Approximately 6-10 weeks after the procedure (for LGG or recurrent high grade glioma or brain metastasis) or first visit after radiation [for newly-diagnosed or transformed high grade glioma (HGG)], the following data will be obtained: admission duration for the MSR, any seizure activity, any readmissions, ED visits, and provider communications (telephone, email, and additional clinic encounters, etc.), as well as for tolerance of the AED by clinical history and neurological examination. Reasons for readmission and ED visits will also be noted. All of these data are only obtained if relevant during the 30-day post-procedure time. Patients will be provided a physical calendar to document any of the above, or provided access to the Research Electronic Data Capture™ (REDCap™) calendar, based on the patient's preference.

7.1.4 Adverse Events of Special Interest (AESI)

The occurrence of adverse events of special interest (AESIs) will be recorded only for the 30-day post-procedure phase.

AESIs for this study will be graded using the National Cancer Institute's (NIH) Common Terminology Criteria for Adverse Events (CTCAE) v4 and are the following: any grade of seizure, dizziness, somnolence, cognitive

disturbance, nausea, vomiting, ataxia, nystagmus, suicidal ideation, suicide attempt, anxiety, irritability, depression, psychosis and personality change (e.g. aggression).

7.1.5 Safety Considerations

LEV has even been associated with a greater suicide risk in those with a psychiatric history. The latter risk depends primarily on the psychiatry comorbidities of the patient. The potential risk for the patient will be discussed in detail with the patient and family. See Section 5.2.5 for additional AED side effects.

7.1.6 Missed Doses

Missed doses will be taken as soon as remembered. Patients will be provided a calendar to track doses taken in order to determine compliance.

7.1.7 Concomitant Medications

Given the lack of significant drug-drug interactions with new generation AEDs, concomitant medications will not be limited. If needed, patients will be initiated on chemotherapy, radiation therapy and corticosteroids, per standard of care. Concomitant medications will be recorded by the study team from time of enrollment and during the 30-day follow up.

7.1.8 Randomization

Upon consent, patients will be randomized in REDCap™ to receive either LCM, LEV, or no AED. Randomization will be stratified by suspected histologic grade (LGG vs HGG) based on MRI review by the treating neurosurgeon and/or neuro-oncologist. A stratified permuted block randomization algorithm will be used assign patients to treatment arms.

7.2 Rationale for Selection of Dose and Treatment Duration

Dosing was based on standard dosing approved by FDA for each AED. Treatment duration of approximately 6 to 10 weeks correlates with when the patients will most likely be guaranteed follow up after surgery, an optimal time to evaluate whether an AED should be continued or not.

7.3 Definition of Evaluable Subjects, On Study, and End of Study

Any patient that has been consented and randomized to the trial will be included in all analyses with the exception of those deemed non-evaluable as described in Section 10.5.2.

Subjects will be considered on study once they have signed the informed consent form.. Subjects will be considered off study when they have been evaluated approximately 6 to 10 weeks post MSR and once their calendar has been submitted.

7.4 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.3.

8 STUDY DRUGS

8.1 Names, Classification, and Mechanism of Action

See Section 5.2

8.2 Packaging and Labeling

Package Inserts are uploaded in eIRB Section 8.

8.3 Supply, Receipt, and Storage

Local Pharmacy and/or Duke Hospital Pharmacy.

8.4 Dispensing and Preparation

Medications will be prescribed for subjects and obtained from the subject's local pharmacy or mail-order pharmacy as per the subject's health insurance plan. Subjects receiving medication after hospital admission will have medication dispensed from Duke Hospital Pharmacy.

9 SUBJECT ELIGIBILITY

9.1.1 Inclusion Criteria

1. Patients with a suspected diagnosis of new, recurrent, or transformed glioma (WHO grade I-IV) or brain metastasis scheduled for MSR at DUMC;
2. Safe for surgery per treating neurosurgeon;
3. Due to the potential implications of the treatment on the developing CNS, all patients must be ≥ 18 years of age at the time of entry into the study;
4. Laboratory Studies:
    a. Total bilirubin, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Alkaline Phosphatase (ALK) ≤ 1.5 x upper limit of normal (ULN)
    b. Creatinine ≤ 1.5
5. A signed informed consent form approved by the Duke University Institutional Review Board (IRB) will be required for patient enrollment into the study. Patients or their Legally Authorized Representative (LAR) must be able to read and understand the informed consent document and must sign the informed consent indicating that they are aware of the investigational nature of this study. Treating physicians at the time the protocol is presented are able to determine based on their clinical judgment whether patients lack the capacity and require a LAR to sign the consent form.
6. Patients of child bearing potential or with partners of child-bearing potential must agree to practice recommended contraceptive methods to prevent pregnancy during treatment and for 1 month after the last dose of AED for women and men.

9.1.2 Exclusion Criteria

1. Pregnant or need to breast feed during the study period (Negative urine β-HCG test required), or unable to maintain use of contraception while on study and for 1 month after the last dose of AED;
2. Patients already on AED(s) specifically to treat seizures will be excluded. Those patients taking AEDs for any diagnosis other than seizures will be included (e.g. Gabapentin for neuropathic pain, Topiramate for migraine, benzodiazepines as sleeping aid, etc). Patients taking AEDs for seizure prophylaxis and without clear history of seizures will be included;
3. Known history of epilepsy/seizure disorder;
4. Known history of dependency/abuse of psychopharmaceuticals, alcohol, illicit drugs or narcotics;
5. Any significant medical or psychiatric illness that cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate therapy, per the discretion of the treating investigator;
6. Known allergy to LCM or LEV.

10 SCREENING AND ON-STUDY TESTS AND PROCEDURES

Table 2: Schedule of Events

Description	Screening at pre-operative visit up to 48 hours prior to MSR	First post-procedure visit (LGG) or first visit after radiation (HGG)
Week		6-10*
Day	0	
General Evaluations		
Physical Exam	X	X
Neurologic Exam	X	X
Evaluation as candidate for MSR	X	
Adverse Events		X
Laboratory Evaluations		
CBC with differential	X	X
CMP	X	X
Urine Pregnancy Test	X	
Disease Evaluations		
Seizure-related readmissions, ED visits, provider communications, duration of admission for MSR		X

*While patients will be assessed between 6-10 weeks post-procedure, only endpoint data pertaining to the first 30 days post-procedure will be recorded in the source documentation and in the database.

10.1 Screening Evaluations

The baseline physical and neurologic examination along with standard of care blood work will be performed and documented by the clinical team and verified by the study team during the pre-operative clinic (or ED) visit. All subject screening data is standard of care evaluations that occur for all patients being seen for possible MSR of suspected LGG or HGG (newly-diagnosed, recurrent, or transformed).) An informed consent must be signed by the patient before any research-related procedure takes place.

Pre-treatment evaluations will include the following:

- History and physical exam, as part of pre-operative evaluation
- Laboratory Evaluations:
  - CBC with differential
  - CMP
  - Urine pregnancy test, if appropriate (serum pregnancy if unable to obtain urine)

If a subject is found to be ineligible to participate in the study, minimal records regarding the subject and the reason for screen failure will be retained in the study database.

The only data collected pertains to the 30-day post-procedure period, however, data may be delayed in collecting due to the standard of care clinic visit schedule.

10.2 Study Period

Day 0 and prior (diagnosis): occurring at least within 48 hours prior to MSR

- Randomization
- Initiate AED, per Section 7.1.1 (LCM 100mg BID or LEV 1000mg BID)
- Characterize seizure type, if applicable, (i.e., simple partial, complex partial, or generalized)

Week 0-6

- Management of AEDs for any seizure events or adverse events will be left at the discretion of the treating physician. If side effects occur, adjusting dosing of current AED before changing AEDs is recommended.

Week 6-10: at the first planned post-procedure visit (LGG or brain metastasis) or first visit after radiation (HGG), the following study endpoint data will be collected only for the 30-day post-procedure time period

- Collection of calendar, if not already obtained from the REDcap database
- CMP and CBC with differential to assess resolution of toxicity
- AESI (please see Section 7.1.4)
- Number of readmissions, ED visits, provider communications during the 30-day post-procedure phase
- Number of dose adjustments, additions or discontinuations of AED(s) during the 30-day post-procedure phase
- Initiate weaning of the AED per discretion of the treating physician, for example:
    - LCM 100/50mg x1 week, 50/50mg x 1 week, 50mg daily x 1 week, then off
    - LEV 1000/500mg x1 week, 500/500mg x 1 week, 500mg daily x 1 week, then off

10.3 Follow-up Period

Subjects will be followed for seizure-related healthcare encounters at the times described above (See Section 10.2). Adverse events will be collected and recorded for the first 30 days post-procedure (See Sections 7.1.3 and 7.1.4 for details).

10.4 End of Study

The study will be considered complete once enrollment has been met, follow-up evaluations on all subjects have been conducted, and data analysis is concluded. The study may also be terminated early for any reason by the PI-sponsor.

Subjects that are lost to follow-up will be documented in the patient record and in the REDCap™ database. In the REDCap™ database, the subject will be marked as "Patient Status Unknown," along with a corresponding explanation, if any. This status may also be documented on the "Off Study Form" in the REDCap™ database.

10.5 Early Withdrawal of Subject(s)

10.5.1 Criteria for Subject Discontinuation from the Study

Subjects may voluntarily withdraw from the study at any time. The primary investigator (PI) may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Non-compliance of the subject
- Administrative issues
- Concerns for patient safety

10.5.2 Replacement of Non-evaluable

A subject who withdraws study participation between randomization and the MSR will be excluded from primary analysis. An additional patient will be randomized to the study to replace that subject to meet the sample size requirements.

10.6 Study Assessments

Study assessments listed here are obtained per standard of care and are only documented for purposes of eligibility assessment.

10.6.1 Medical History

Standard medical history will be obtained and documented per institutional guidelines.

10.6.2 Physical Exam

Standard physical exam and neurological assessment will be conducted and documented per institutional guidelines.

10.6.3 Laboratory Evaluations

The timing of standard laboratory assessments that will be obtained during the course of the study is given in the Schedule of Events Table 2 in Section 10. A list of each evaluation and what they include is below.

- CBC with differential
- CMP
- Urine pregnancy test, if appropriate (serum pregnancy test if unable to obtain urine)

11 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or serious adverse event (SAE) has occurred.

11.1 Adverse Events

An AE is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding) or symptom temporally associated with the use of the AED, whether or not related to use of the AED.

From the time the subject initiates AED therapy through the time the subject is off study (as defined in Section 7.3), all AESIs must be recorded in the REDCap™ database AE electronic Case Report Form (eCRF). Adverse events which are not an AESI will not be collected.

AESIs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. If CTCAE grading does not exist for an AESI, the severity of the AESI will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

11.1.1 Reporting of AEs

A database of all AESI will be maintained in REDCap™. Adverse events which are not an AESI will not be collected. The event will be categorized by organ system, relationship to treatment, its grade of severity, and resolution. The PI and study statistician will periodically review the collective adverse events with the intention of identifying any trends or patterns in toxicity. If any such trends are identified, depending on their severity and frequency, a protocol amendment will be considered.

11.2 Serious Adverse Events

An AE is considered “serious” if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect

- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

11.2.1 Reporting of SAEs

All serious and unexpected adverse events should be reported immediately to Dr. Annick Desjardins (pager 919-970-7348 or her designee (919-684-8111). Only adverse events that the Duke Sponsor-Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e. more likely than not) related to the research must be reported to the Duke IRB. Those adverse events will be submitted in the electronic IRB (eIRB) system, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related adverse event;
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the research than unrelated.

11.3 Quality Assurance Program

The Neurosurgery Quality Assurance Program (QAP) ensures adequate oversight for all types of human subject research that are under the Duke Neurosurgery-Clinical Research Unit (NS-CRU) supervision. Oversight begins with an effective scientific and feasibility review process accompanied by a robust data safety and monitoring plan.

The Duke Cancer Institute's Safety Oversight Committee (DCI SOCOMM) in concert with the NS-CRU QAP Monitoring Team (see Section 12.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

This clinical research study will be monitored both internally by the PI and by the Department of Neurosurgery. In terms of internal review, the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

The data and safety monitoring responsibilities are shared amongst Investigators, Neurosurgery Oversight Team, Neurosurgery Research Working Group and Duke Research Compliance Assurance (RCA) team.

The studies that are higher-risk (risk level II, III and IV), prospective studies that consent subjects will be subjected to internal reviews. The following table (table: 1) describes the risk levels for the studies:

	Risk Level I	Risk Level II	Risk Level III	Risk Level IV
Study funding source	Investigator Initiated Trial	Investigator Initiated Trial	Investigator Initiated Trial	Investigator Initiated Trial
Trial design	Retrospective chart reviews Exempt data/tissue collection	• Prospective - Specimen and data collection studies • Single Arm study - off label use of approved drug/device	• Single Arm study – Multiple IND drug regimen • Multiple arms (cohorts or treatments) – No Randomization • Multiple arms – simple randomization ph II or I/II studies	Multiple arms - with Randomization – single or double blinding
Complexity of the study regimen	No drug or device involved	FDA approved drug/ Device Non-Significant Risk Device	• Single drug/ IND study • Multiple drug/ IND study • IDE device study • IND + Device combination study	• Single drug/ IND study • Multiple drug/ IND study • IDE device study • IND + Device combination study
Toxicity profile/Subject risk profile	Low to No toxicity profile	Known toxicity profile	Potentially significant toxicity profile	Expected high toxicity profile

Table 1: Different Risk Levels for Investigator Initiated Trials

The study risk assessment is done by the PI and the study team during the protocol development process. The expectation is that all Investigator Initiated perspective interventional studies have a monitoring plan written in the protocol. This monitoring plan will be reviewed and approved by the scientific reviewers during the scientific review of the study.

Other types of studies that might be subjected to internal reviews are listed below:

- Studies being conducted by a new PI or a new study staff or both;
- Sponsored interventional studies for which Duke NSCRU is amongst the highest enrolling sites;
- Any phase III interventional studies that are close to receiving an FDA approval for the IND/IDE it is testing.

Any study that does not fall under the above mentioned criteria are low-risk studies (e.g., retrospective chart reviews). Those studies may be monitored only for data integrity, completeness and/or maintenance of all applicable regulatory approvals.

This study falls under the Risk Level III category. This means that this study is more interventional in nature and may require a higher scrutiny. The studies that fall into this category will have the following oversight:

- Review of the subject chart and 100 % of the data of the first 2 subjects enrolled.
- Review of the Regulatory binder after the first 2 subjects are enrolled.
- Drug/Device accountability logs after the first 2 subjects are enrolled and have received a study intervention.
- Ongoing reviews will be done quarterly until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk, and will include:
  - Review of the informed consents of all subjects enrolled
  - Subject charts, drug/device accountability and specimen collection process of 20 % of the subjects enrolled on the study
  - Review of any major deviations or safety events
  - Review of the enrollment status
- Ongoing reviews of the regulatory binders will be performed annually.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of the NS-CRU QAP, DUHS and DCI leadership, the DCI Cancer Protocol Committee (CPC), the SOCOMM, the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the QAP Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

12.2 Audits

The Duke Office of Audit, Risk and Compliance (OARC) may conduct audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

12.3 Data Management and Processing

12.3.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, drug calendars, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the “Regulatory Binder,” which includes but is not limited to continuing reviews, safety events, and amendments, approved and signed informed consent forms, and College of American Pathologists (CAP), Commission on Office Laboratory Accreditation (COLA), and Clinical Laboratory Improvement Act (CLIA) laboratory certifications.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries, drug calendars or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

12.3.2 Case Report Forms

Paper Case Report Forms (CRFs) will be created for purposes of eligibility and data collection. The information from the paper CRFs will then be entered into the eCRF in REDCap™.

The eCRF will be the primary data collection document for the study and is developed in conjunction with statistical oversight. The eCRFs will be updated in a timely manner following acquisition of new source data. Only study personnel trained for accessing and entering data in REDCap™ are permitted to make entries, changes, or corrections in the eCRF.

An audit trail will be maintained automatically by the electronic CRF management system, REDCap™. All users of this system will complete user training, as required or appropriate per institutional requirements and other regulations.

12.3.3 Data Management Procedures and Data Verification

Access to electronic databases will be managed by the Data Manager.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data management team and the statistical team will cross-reference the data to verify accuracy. Missing or implausible data will be brought to the attention of the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

12.3.4 Coding

All medical terms will be coded using CTCAE v.4.

12.3.5 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution;
- Review of site study records for completeness.

13 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

13.1 Analysis Sets

All evaluable subjects will be included in efficacy and safety analyses.

13.2 Patient Demographics and Other Baseline Characteristics

Socio-demographic and clinical characteristics of patients enrolled onto this study will be summarized. For categorical variables, frequencies and percentages will be provided. Means with standard deviations and medians/percentiles will summarize non-categorical variables.

13.3 Treatments

The number of patients treated on each arm (LCM, LEV, or no AED) will be calculated.

13.4 Primary Objectives

The primary objective of this study is to assess the impact of LCM, LEV or, no AED in patients undergoing MSR for suspected new, recurrent or transformed glioma (WHO Gr I-IV) or brain metastasis. The basis for making this assessment will be the number of ED visits or readmissions within 30 days of MSR.

13.4.1 Variables

Percentage of subjects with an emergency room visit or re-hospitalization within 30 days after MSR.

13.4.2 Statistical Hypothesis, Model, and Method of Analysis

Though the percentage of patients who are re-hospitalized or have an emergency room visit during the 30 days post-MSR will be calculated within each treatment group, the primary comparison will combine outcome observed within the LCM and LEV arms. The statistical comparison will assess the impact of AED (LCM or LEV) relative to no AED on this endpoint.

Let us define P1 and P2 as follows:

P1 = Percentage of patients treated prophylactically with AED (LCM or LEV) who are re-hospitalized or have an emergency room visit during the 30 days post-MSR

P2 = Percentage of patients not prophylactically treated (i.e. no AED) who are re-hospitalized or have an emergency room visit during the 30 days post-MSR

Given that current guidelines recommend against peri-operative seizure prophylaxis, we are interested in showing that AED is better than No AED, or $P1 < P2$, or $0 < P2 - P1$. Hence, the hypothesis we will be testing is:

$$H0: \theta \leq 0 \text{ vs } H1: \theta > 0$$

where $\theta = P2 - P1$. A one-tailed test using a large-sample Z test will be conducted given the directional hypothesis that is being posed.

With stratification for suspected grade (LGG vs HGG), the Cochran-Mantel-Haenszel test statistic will compare patients who do and do not receive AED with respect to the proportion of patients re-hospitalized or have an emergency room visit during the 30 days post-MSR.

An interim analysis will be conducted half way through the study to assess whether early study termination is appropriate. An O'Brien-Fleming boundary will provide guidance for making that assessment. This interim analysis will determine whether the hypothesis can be rejected or accepted at that time. See section 13.7 and 13.8 for further detail.

An intent-to-treat philosophy will be used in generating statistical analyses.

13.4.3 Handling of missing values, censoring, and discontinuations

Given that the length of follow-up required after brain surgery is limited to 30 days in terms of data collection, we anticipate there being a minimal amount of missing primary outcome data.

In the event that a patient does not complete the 30 day follow-up due to death, the patient will be treated as if they were either re-hospitalized and/or visited the emergency room.

If a subject withdraws study participation between randomization and the MSR, that subject will be excluded from primary analyses. An additional patient will be randomized to the study to replace that subject to meet the

sample size requirements for the study. It is not believed that the knowledge of treatment group assignment would influence a patient's decision to withdraw from the study.

13.5 Secondary objectives

This study has one secondary objective which is to assess the safety and tolerability of LCM and LEV.

Adverse events will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4. For each type of toxicity, the maximum grade experienced by the patient will be summarized with frequency distributions based upon all AESIs. Of particular interest are those adverse events of special interest (AESI), as defined in section 7.1.4, that occur within 30 days afterMSR.

The percentage of patients experiencing any grade adverse events of special interest within 30 days of MSRwill be summarized in each of the 3 treatment arms, and compared using chi-square tests. If AED is shown to have fewer re-hospitalizations or ED visits, then a pairwise comparison of LCM and LEV is of particular interest.

13.6 Exploratory Objectives

The 6 exploratory objectives include an examination of the duration of admission stay, the number of provider communications, use of intraoperative AED, seizure occurrence, modifications of AED administration and risk factors for post-MSR seizure.

13.6.1 Exploratory Objective: Duration of Admission Stay

For each patient accrued to this study, the duration of the initial admission stay for the MSR will be calculated as the time interval between the date of MSR and date of discharge. A Wilcoxon rank sum test will compare the combined AED groups versus the no AED group with respect to the distribution for the duration of the initial admission stay. Reasons for an extended initial stay greater than 2-3 days will be summarized by treatment group.

13.6.2 Exploratory Objective: Number of Provider Communications

The number of provider communications (email, telephone, or additional clinical visits) during the 30 days post-MSR will be determined for each patient. Within each group, the distribution of the total number of provider contacts will be summarized with a frequency distribution. Either a Wilcoxon rank sum test or a chi-square test will compare AED (combined) and no AED groups.

13.6.3 Exploratory Objective: Usage of Intraoperative AED

Whether or not intraoperative AED is administered will be assessed for each patient, and the proportion of subjects requiring an intraoperative AED will be calculated within each group. AED (combined) and no AED groups will be compared with respect to the percentage of subjects requiring an intraoperative AED with a chi-square test.

Details concerning the type and dose of AED will also be summarized descriptively.

13.6.4 Exploratory Objective: Seizure Occurrence

The percentage of patients experiencing post-MSR seizures will be assessed within each arm. A chi-square test will compare AED (combined) to no AED groups relative to this outcome.

In addition, the distribution of the number of seizures experiences over the 30 day period will be generated within each arm. A Wilcoxon rank sum test will compare AED (combined) and no AED groups with respect to the number of seizures reported.

13.6.5 Exploratory Objective: Changes in AED Administration

The frequency of changes in AED dose, type of AED, addition or discontinuation of AED will be described.

13.6.6 Exploratory Objective: Risk Factors for Post-MSR seizure

Well-known risk factors predictive of seizure will be assessed (age, frontal/temporal/parietal tumor locations, cortical vs. subcortical location, tumor size, low grade vs. high grade tumor, extent of resection [GTR vs. sub-total resection (STR) vs. biopsy] [71-77]. Other potential risk factors such as tumor genetics will also be collected, such as, but not limited to: IDH1 mutation, TERT, ATRX, EGFRvIII. The association between each of these factors and the occurrence of post-MSR seizure will be examined within a logistic regression model.

Depending upon the prevalence of post-MSR seizures, a multivariate logistic regression analysis may be conducted that examines the joint effect of these factors, as well as treatment assignment and treatment interactions on outcome. To maintain validity and stability of such modeling, the number of predictors for consideration in a multivariable logistic model will be no more than 1 predictor for every 10 seizures.

13.7 Interim Analysis

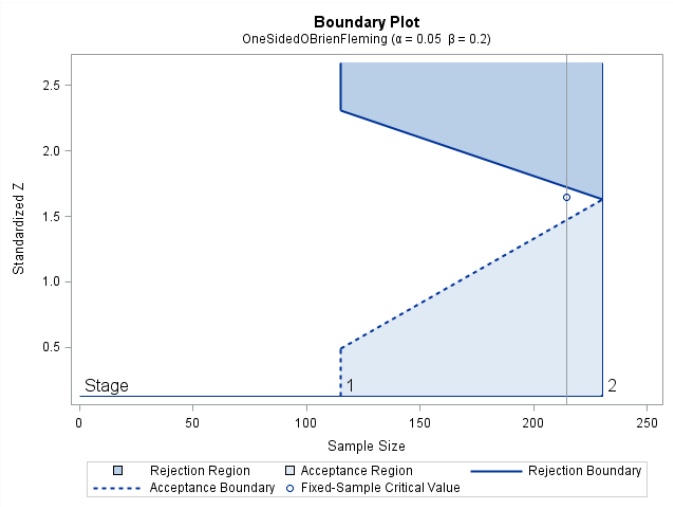
After 116 accrued patients have completed their 30 day follow-up post-MSR, an interim analysis will be conducted. This analysis that is conducted halfway through the study will assess whether accrual could be terminated early and whether the null or alternative hypothesis could be accepted.

The O'Brien-Fleming boundaries that are used in the decision-making are defined in terms of a Z-statistic. Those boundaries are provided below for the interim and final analysis (SAS PROC SEQDESIGN).

Stage	Total N Accrued	Total Assigned to AED Groups	Total Assigned to No AED Group	Reject Null Hypothesis * if:	Accept Null Hypothesis ** if:
1	116	58	58	Z > 2.31015	Z ≤ 0.48887
2	232	116	116	Z > 1.63351	Z ≤ 1.63351

*Reject null hypothesis and conclude that AED better.
**Accept null hypothesis and conclude that AED is <u>not better.</u>

These boundaries are presented graphically below. The interim analysis occurs at the point on the x-axis labeled as (1), and the final analysis occurs at the point labeled as (2).



The standardized Z statistic presented in the boundaries above is a function of the following difference: Percent of no AED patients with re-hospitalization or ED visit – Percent of AED patients with re-hospitalization or ED visit. The denominator of the Z statistic is a measure of the variability of this difference.

- If the observed percentage of patients with re-hospitalization or ED visits is greater within the no AED group than in the AED group, then the Z statistic will be positive.
- If the observed percentage in the no AED group is less than that in the AED group, then the Z statistic will be negative.
- If there is no difference between groups in the observed percentage of patients with re-hospitalization or ED visits, then the Z statistic will be 0.

The dark blue region in the figure above is where one concludes that AED is better than no AED; whereas, the light blue region is where one concludes that AED is not better than "no AED" (i.e. they are the same or no AED is better). At the time of the interim analysis, the study will be terminated if $Z > 2.31013$ (i.e. observed percentage within the no AED group is much larger than that in the AED group) and the conclusion will be that AED treatment is better. Also at the time of the interim analysis, the study will be terminated if $Z \leq 0.48887$ (i.e. observed percentage within the AED group is greater than that observed in the no AED group, or about the same with AED or no AED) and the conclusion will be that AED treatment is not better. If the Z calculated at the time of the interim analysis is between 0.48887 and 2.31013, the remaining patients will be accrued to the study. At the time of the final analysis, the threshold for decision-making is Z=1.63351.

If the accrual is unbalanced at the time of the interim analysis, the boundaries stated here may need to be modified slightly.

Though the verb "terminated" is used above in the description of the monitoring rules, these rules should be viewed as guidelines for the determination of whether accrual should be terminated or not. Additional factors may be considered in the determination of whether accrual should continue after the interim analysis.

13.8 Sample Size

Eligible subjects will be randomized to one of 3 treatment arms (LCM, LEV, or no AED) using an allocation ratio of 1:1:2. Randomization will be implemented using a permuted block algorithm. Randomization will be stratified by suspected grade of glioma (high vs low grade) or brain metastasis..

The experience of subjects in the LCM and LEV groups will be combined to estimate the percentage of subjects with an ED visit or readmission within 30 days of MSR after seizure prophylaxis pre-surgery. That outcome will be compared to the same outcome observed among patients in the no AED group.

In designing this study, we have considered the following background information:

- In a recently conducted retrospective review of Duke's experience with AEDs and MSR (Pro00047350 Descriptive and Cost Analysis of Post-procedure Anti-Epileptic Drugs in Malignant Glioma), the experience of patients newly diagnosed with malignant glioma and without prior seizure history or AED use was examined. Among those patients who were prophylactically treated with LEV before MSR, 12% of subjects were re-hospitalized or visited emergency room within 30 days post-MSR.

- Published literature indicates that the risk of post-MSR seizure in MG patients without AED prophylaxis ranges from 2.3% up to 35%, particularly in glioblastoma (GBM).[75,77,78]

Therefore in designing the study we have assumed that the percentage of patients with re-hospitalization or ED visits within 30 days post-MSR is 12% in both the LCM and LEV groups. We have also designed the study to detect an increase in re-hospitalization or ED visits to 25% within the no AED group.

Additional assumptions for the power calculations include the following:

- One-tailed test conducted so that the overall type I error rate if 0.05. This type I error rate accounts for one interim analysis.
- Power = 80% under the alternative where the true outcome is 12% in the AE group (combined) and 25% in the no AED group.
- One interim analysis half way through the study that allows early termination with either acceptance or rejection of the null hypothesis.

Under these conditions, there is a need to randomize and follow 232 subjects for 30 days. An interim analysis as described in Section 13.7 will be conducted after 116 patients (SAS PROC SEQDESIGN).

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS IRB and DCI CPC for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored in a study-specific consent binder. A copy of the informed consent will be sent to Health Information Management and an additional copy of the informed consent form will be provided to the subject.

14.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database, REDCap™, which is housed in an encrypted and password-protected file on a secure network drive. Access to electronic databases will be managed by the Data Manager. The security and viability of the Information Technology (IT) infrastructure will be managed by Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS Human Research Protection Program (HRPP) policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.5 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 12.

14.6 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

14.7 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least six years after study completion (Duke policy).

14.8 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/Investigational Ethics Committee (IEC).

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