SPRING
Seizure **PR**ophylaxis **IN G**lioma

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Synopsis

Protocol ID:	SPRING
Protocol Title:	**S**eizure **PR**ophylaxis **IN G**lioma
Trial Description:	A phase III randomised trial comparing prophylactic levetiracetam versus no prophylactic anti epileptic drug in patients with newly diagnosed presumed supratentorial (cerebral) glioma.
Development Phase:	Randomised phase III
Primary Objective:	To determine 'In seizure-naive newly diagnosed cerebral glioma patients undergoing surgery, does prophylactic levetiracetam pre-operatively and for at least 1 year, produce a meaningful (>50%) reduction in the risk of developing seizures, when compared with standard care (No AED)?' The Primary Outcome is one year risk of first seizure.

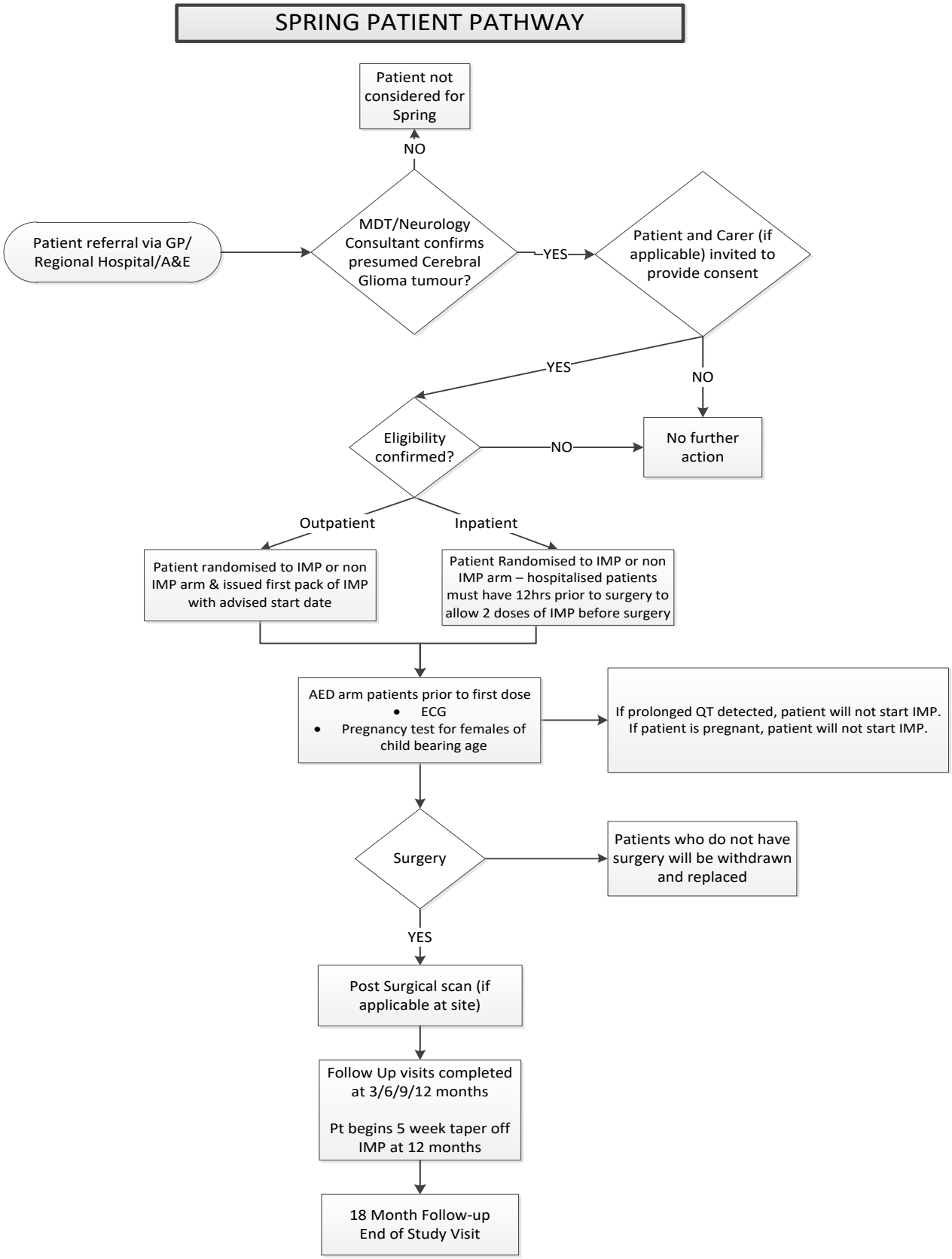
Secondary Objectives:

- To determine whether prophylactic levetiracetam increases time to first seizure.
- To determine whether prophylactic levetiracetam increases time to first tonic-clonic seizure.
- To determine whether prophylactic levetiracetam affects mood, personality, fatigue and memory.
- To determine whether levetiracetam positively influences the severity of first seizure should it occur.
- To determine whether levetiracetam impacts on quality of life.
- To determine whether levetiracetam impacts on progression free survival.
- To determine whether levetiracetam impacts on overall survival.
- To determine whether levetiracetam given prophylactically reduces costs to the NHS and personal social services (PSS) over the 12 months trial follow-up.
- To determine the cost-effectiveness of prophylactic levetiracetam measured as incremental cost per QALY at 12 months and modelled over estimated survival.

Study Design:	Two arm, multicentre phase III randomised trial of prophylactic anti-epileptic drug (Levetiracetam) versus no anti-epileptic drug (AED) (comparator) in patients with suspected cerebral glioma. Randomly assigned - 1:1 basis. Patients will be followed up for 12 months. The trial will end when the last living patient has completed their 12 month follow up visit.

Patient Accrual:	804 patients will be recruited over a three-year period at sites in the UK.
Final Analysis:	The final analysis will be performed when all patients have been followed up for a minimum of one year.
Interim Analysis:	An interim analysis will be performed at the end of the internal pilot period (12 months after first site opened). The aim of the analysis is to establish that recruitment in to the study is achievable within time frames specified and formal stop/go criteria will be assessed.

Patient Pathway



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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AED	Antiepileptic drug
AR	Adverse Reaction
CI	Chief Investigator
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EoL	End of Life
EQ-5D-5L	EuroQol five-dimensional 5 Level questionnaire
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRQoL	Health Related Quality of life
HGG	High Grade Glioma
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Approval System
KPS	Karnofsky Performance Status
LAEP	Liverpool Adverse Events Profile
LIES	Liverpool Impact of Epilepsy Scale
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PHQ-9	Patient Health Questionnaire-9
PHS	Public Health Scotland
PI	Principal Investigator
PPI	Patient and Public Involvement
PO	Per Oral
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCTRU	Scottish Clinical Trials Research Unit
SDV	Source Data Verification
SG	Standard Gamble
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUDEP	Sudden Unexpected Death in Epilepsy
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVFT	Semantic Verbal Fluency Test
TMG	Trial Management Group
TSC	Trial Steering Committee

1. INTRODUCTION

1.1. Background

Gliomas and seizures

Gliomas are the most common type of primary brain tumour. There are approximately 6,000 new cases of glioma diagnosed in the UK each year [1].20% of patients who have a suspected glioma will present with a new onset seizure prior to surgery. Of the remaining 80%, seizures will also occur, post-surgery or at some later stage prior to death in 30-50% of cases [2, 3]. The standard of care for glioma patients who present with seizures includes the administration of antiepileptic drugs (AEDs) [4]. There is, however, no consensus regarding the administration of prophylactic AEDs to patients with cerebral glioma who have not had seizures. Increasingly, neurosurgeons prescribe AEDs [5] although Guidelines from Society for Neuro-Oncology and European Association for Neuro-Oncology and American Academy of Neurology (ANN) recommend no prophylactic AEDs, based on historical randomised controlled trials of first generation AEDs (Table 1). Recent AEDs have fewer allergic complications and drug-drug interactions. A new trial is required to give up to date evidence to inform neuro-surgeons, neuro-oncologists, neurologists and patients.

Table 1 - Previous studies of prophylactic AEDs in brain tumour

Study	Total number of patients	Number of patients on AEDs	AEDs	Outcome
Boarini *et al.*[6]	71	33	Phenobarbitone & phenytoin	Odds ratio for seizure 0.41 (95% CI 0.14 – 1.19). No patients with therapeutic AED levels had seizures; 18% of untreated patients did.
Moots *et al.*[7]	36	4	Phenobarbitone & phenytoin	No seizures in AED group compared with 31% in untreated patients (p=0.60).

The few prospective studies reported to date (Table 2) have included patients with gliomas, brain metastases and meningiomas. The results of these studies have also been inconclusive.

Table 2 – Prospective studies using AEDs in brain tumour

Study	Total number of patients	Number of patients on AEDs	AEDs	Outcome
Franceschetti *et al.*[8]	63	41	Phenobarbitone & phenytoin	Odds ratio for seizure in AED group 0.36 (95% CI 0.07-1.76).
Forsyth *et al.*[9]	100	46	Phenobarb & phenytoin	Odds ratio for seizure in AED group was 0.82 (95% CI 0.33-2.01).
Glantz *et al.*[10]	74	37	Valproate	Odds ratio for seizure in AED group was 1.7 (95% CI 0.6-4.6).
North *et al.*[11]	81	42	Phenytoin	Odds ratio for seizure in the AED group was 1.85 (95% CI 0.56-6.12).

Many brain tumour patients are treated with AEDs partly because they have had a craniotomy and there is an increased incidence of seizures following craniotomy. It is unclear, however, whether prolonged prophylactic AED therapy reduces the frequency of seizures after craniotomy. Foy *et al.* [12] completed a prospective trial involving 276 consecutive supratentorial craniotomy patients (including 50 with meningiomas) who were randomised postoperatively to receive AEDs (carbamazepine or phenytoin) or no treatment. There was no difference in the incidence of seizures (37%) or death between the two groups, suggesting that prophylactic AED therapy may not be routinely necessary after craniotomy. In contrast, a systematic review and meta-analysis of six controlled trials was performed by Kuijlen *et al.* [13] who determined that prophylactic AEDs tended to prevent postoperative convulsions, but this effect was not statistically significant (p = 0.1, one-tailed).

In 2000, the Quality Standards Subcommittee of the American Academy of Neurology reviewed the evidence concerning the efficacy of prophylactic AEDs in patients with all brain tumour types [14]. Because the numbers of patients in the studies reviewed were small, they performed a meta-analysis of the four available randomised studies addressing prophylactic AEDs pre-operatively for brain tumour. They concluded that there was no evidence of a significant benefit of prophylactic AEDs and recommended as a practice standard that AEDs should not be administered pre-operatively in cases with suspected brain tumour. A shortcoming of their meta-analysis relative to glioma patients, however, is that it only included 110 glioma patients and 218 non-glioma tumour patients (145 brain metastases, 46 meningiomas and 17 sellar tumours). Because the majority of patients were those with metastatic tumours, a patient population with a lower incidence of seizures and a shorter life

expectancy than patients with gliomas, the efficacy of prophylactic AEDs in glioma patients in particular remains an open question [15]. The American Association of Neurology guidance discourages the use of prophylactic AEDs, but this guidance remains largely ignored by this clinician group in the US [16,17].

1.2. Investigational Medicinal Product

Levetiracetam is an antiepileptic drug available as 250mg (blue) and 500mg (yellow) tablets for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C8H14N2O2 and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). Levetiracetam tablets contain the labelled amount of levetiracetam. Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyethylene glycol 3350, polyethylene glycol 6000, polyvinyl alcohol, talc, titanium dioxide, and additional agents listed below:

- 250mg tablets: FD&C Blue #2/indigo carmine aluminium lake
- 500mg tablets: iron oxide yellow

1.3. Pre-Clinical Data

In vitro studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of Ntype Ca2+ currents and by reducing the release of Ca2+ from intraneuronal stores. In addition it partially reverses the reductions in Gamma-Aminobutyric Acid and glycine-gated currents induced by zinc and β- carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

1.4. Clinical Data

Levetiracetam is an effective first line agent for treatment of focal seizures and secondary generalised seizures [18]. Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, noninferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. Levetiracetam is the current drug of choice in brain tumour related epilepsy [19]. It has been

shown to be similarly effective as phenytoin in a small Randomised phase II pilot study in brain tumour patients and has fewer side effects [20]. The effective dose of prophylactic levetiracetam at preventing seizures has not been established, but in adults with refractory non-tumour related epilepsy, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7 %, 31.6 % and 41.3 % for patients on 1000, 2000 or 3000mg levetiracetam respectively and of 12.6% for patients on placebo. In double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States comparing Keppra 1000mg/day (N=97), Keppra 3000mg/day (N=101), and placebo (N=95) in adults with focal epilepsy, the reduction in mean over placebo in weekly frequency of partial seizures was 26.1% for 1 gram/day and 30.1% for 3 gram/day [21].

In summary, people with brain tumours have focal epilepsy. Levetiracetam has similar efficacy to carbamazepine in patients with focal epilepsy. Levetiracetam does not have the Cytochrome P450 related interactions or haematological toxicities and rash seen with other first line agents in partial onset seizures. Currently levetiracetam is the drug of choice in brain tumour related epilepsy.

1.5. Trial Rationale

There is no consensus regarding the need for prophylactic AEDs in newly-diagnosed suspected glioma patients who have not experienced seizures. Unfortunately, data regarding prophylactic AED use is scant and inconclusive. Most of the available evidence comes from older, small studies that enrolled patients with brain metastases and benign tumours in addition to gliomas. Furthermore, these studies universally evaluated prophylaxis with first- generation AEDs such as phenytoin, phenobarbital, carbamazepine, and valproic acid. These drugs have higher rates of early adverse effects (such as rash, haematological or liver upset) compared to levetiracetam, and they have important interactions with other drugs including corticosteroids and chemotherapeutics. Levetiracetam is an effective, safe, and well-tolerated medication. It has no known drug interactions and does not require serum level monitoring. It is however, frequently associated with fatigue (15%), behavioural problems (13-38%) and problems with aggression [22]. A definitive clinical trial is needed to determine whether the policy of prophylactic levetiracetam therapy reduces the risk of first seizures in this patient population. In addition, evaluation of the impact of levetiracetam on fatigue, behaviour and aggression is needed in this vulnerable population with already high rates of fatigue, cognitive and behavioural problems. There is some evidence that levetiracetam may worsen these symptoms [23]. There is a need to study this area in a well-designed randomised controlled trial [24,25].

Levetiracetam

Levetiracetam is an antiepileptic drug marketed since 2000. Its novel mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain. Its pharmacokinetic advantages include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver. The

availability of an intravenous preparation is yet another advantage. It has been demonstrated effective as adjunctive therapy for refractory partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures of juvenile myoclonic epilepsy. In addition, it was found equivalent to controlled release carbamazepine as first-line therapy for partial-onset seizures, both in efficacy and tolerability. Its main adverse effects in randomised adjunctive trials in adults have been somnolence, asthenia, infection, and dizziness.

There is some evidence to suggest that levetiracetam may be neuro-protective in brain injury [26] and that it may be associated with improved cognition in brain tumour patients [27].
Lastly, there is some evidence that levetiracetam may inhibit malignant glioma cell proliferation and increase glioma cell sensitivity to the alkylating agent temozolomide [28].

Side effects of Levetiracetam
AED use is associated with many potential side effects that can have a negative impact on a patient's quality of life. Side effects of levetiracetam can be:

- Affecting more than 1 in 10 people - at varied levels of severity are: sleepiness, headache, and running/blocked nose.
- Affecting between 1 in 10 and 1 in 100 people- at varied levels of severity are: off food, low mood or changes in behaviour, anxiety, poor sleep, dizziness, gastrointestinal symptoms (indigestion, loose stools).
- Affecting between 1 in 100 and 1 in 1000 people – weight increase or decrease, change in levels of blood cells, suicidal thoughts, hallucination, mood swings, panic attacks, memory impairment, prickling sensation, coordination problems, amnesia, blurred/double vision, skin conditions, abnormal liver function, muscular weakness and myalgia.
- Affecting between 1 in 1000 and 1 in 10000 people– infection, changes to normal blood levels, hypersensitivity, suicide, personality disorder, uncontrolled involuntary movement, gait disturbance (walking disorder), encephalopathy, delirium, pancreatitis, liver failure, kidney problems, skin disorders, muscle problems, increased delay between heartbeats on Electrocardiogram, seizures aggravated.

Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders.

Overall, 23.8% of brain tumour patients on AED therapy experience side effects severe enough to warrant a change or discontinuation of AED therapy [29]. Although carefully controlled studies are lacking, newer AEDs such as levetiracetam, have more favourable adverse effect profiles [30].

Levetiracetam is a non-enzyme inducing AED and does not interact with dexamethasone, proton pump inhibitors or chemotherapy used in treatment of glioma. The lack of drug-drug interactions with levetiracetam makes it ideal in patients who may be getting glioma chemotherapy. Levetiracetam may interfere with the excretion of methotrexate, a chemotherapy agent used in the treatment of primary Central Nervous System (CNS)

lymphoma, thus potentially causing methotrexate toxicity [31]. Primary CNS lymphoma may mimic glioblastoma on imaging.

Disease Progression

Cognition

Some patients may lose capacity during the study. This generally heralds the "end of life" (EoL) phase of the disease. There is an increased risk of seizures in the EoL phase[32].The EoL phase is associated with a greater risk of seizures than at other times - 37% in last month of life[33]; 29% in the last week of life[34]. A systematic review recommends future research should focus on the role of prophylactic anticonvulsant treatment in the EoL phase, particularly in High Grade Glioma (HGG) patients[35]. HGG patients are those with cerebral gliomas, which are malignant in their growth potential and are associated with poor survival.

During the course of the trial the cognitive abilities of the patients may fluctuate. All patients must be able to provide informed consent on joining the trial, we would then wish to give the patient the option of remaining in the trial and on treatment (if applicable) should they be unable to make decisions at any point during the trial. The aim is to support the patient in shared decision making as far as possible. This would be a reflection of how decisions are made regarding patient care in routine practice.

Seizures and symptoms

Seizures may result in injuries or life-threatening complications such as status epilepticus or aspiration pneumonia. More often, however, seizures restrict patients' independence; driving is prohibited for 12-24 months after a seizure. In low grade glioma you must be seizure free for 12 months before you can drive again. In high grade gliomas you must be seizure free for 24 months before you can drive again. Patients whose jobs involve driving or working in dangerous circumstances (e.g. painters, electricians) become unable to work and suffer financial consequences. Patients also experience debilitating anxiety about whether or when a seizure may occur. In brain tumour patients, seizures can be associated with worsening of other neurologic symptoms, such as weakness or cognitive symptoms [36]. Direct injury to the patient, as well as secondary injuries to others, can occur with seizure activity [37]. 1 in 1000 patients with epilepsy experience SUDEP (sudden unexpected death in epilepsy) [38]. Brain tumour is a risk factor. Prophylactic AEDs may prevent SUDEP or status epilepticus, a life threatening condition, which may be the first manifestation of epilepsy in brain tumour patients [39].

AEDs can also be associated with side effects and symptoms, including fatigue, drowsiness, and cognitive effects such as decreased memory, difficulty concentrating, behavioural problems and low mood. These symptoms may interfere with activity and impair quality of life.

2. TRIAL OBJECTIVES

2.1. Study design

This is a two arm, multicentre, phase III randomised trial of prophylactic anti-epileptic drug (Levetiracetam) versus no anti-epileptic drug (AED) (comparator) in patients with suspected cerebral glioma.

2.2. Primary objective:

To determine 'In seizure-naive newly diagnosed cerebral glioma patients undergoing surgery, does prophylactic levetiracetam pre-operatively and for at least 1 year, produce a meaningful (>50%) reduction in the risk of developing seizures, when compared with standard care (No AED)?'

The Primary Outcome is one year risk of first seizure.

2.3. Secondary objectives:

- To determine whether prophylactic levetiracetam increases time to first seizure
- To determine whether prophylactic levetiracetam increases time to first tonic clonic seizure
- To determine whether prophylactic levetiracetam affects mood, personality, fatigue and memory
- To determine whether levetiracetam positively influences the severity of first seizure should it occur
- To determine whether levetiracetam impacts on quality of life
- To determine whether levetiracetam impacts on progression free survival.
- To determine whether levetiracetam impacts on overall survival
- To determine whether levetiracetam given prophylactically reduces costs to the NHS (National Health Service) and personal social services (PSS) over the 12 months trial follow-up.
- To determine the cost-effectiveness of prophylactic levetiracetam measured as incremental cost per QALY (quality adjusted life year) at 12 months and modelled over estimated survival.

2.4. Definition of Seizure

If the patient has a seizure they should contact their treating team. The patient should be reviewed by a neurologist to confirm whether a seizure has taken place.

For study purposes, confirmed seizures will include any of the following:

1. Simple partial seizures:

    a) with motor symptoms: focal motor movements, versive/postural movements
    b) with sensory symptoms: olfactory sensations
    c) with autonomic signs
    d) with psychic symptoms (e.g. déjà vu, jamais vu)

2. Complex partial seizures
    a) with impairment of consciousness only
    b) with impairment of consciousness plus automatisms (lip smacking, fumbling, etc.)

3. Partial seizures with secondarily generalized seizures
    a) Unconsciousness with generalised clonic movements
    b) Unconsciousness with generalised tonic spasm, without clonic movements
    c) Unconsciousness or staring with one of the following preceding symptoms perceived by the patient:
        - A rising feeling from the abdomen to the throat
        - Smelling of odd scents
        - Stiffening or convulsions in the face or limb(s)
        - Turning the head to one side.

Excluded attacks are those deemed by the treating physician not to be epileptic seizures.

2.5. Patient Reported Outcomes for Quality of Life

This study seeks to establish whether the use of levetiracetam reduces the occurrence of seizures. However, given the potential side effects and symptoms associated with both seizures and the use of AEDs, it will be important to determine whether any determined benefit is associated with improvements in symptoms.

There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as additional indicators of benefit.

The Patient Reported Outcomes will form part of the initial secondary outcome analysis to determine whether there is a difference in Quality of Life (QoL) between the treatment groups. The data will be collected in line with clinic visits at pre surgery (baseline), 3 months, 6 months, 9 months and 1 year.

Patient Related Outcome Objectives

- To evaluate longitudinal changes in symptom measures and determine the impact of the use of AEDs on these parameters.
- To measure symptom burden over the course of the study period (one year) to evaluate differences between patients' individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between those not taking prophylactic medication versus those on levetiracetam.
- To describe the variability of symptom severity longitudinally over the follow-up period.

Patient Related Outcome Instruments

LAEP (Liverpool Adverse Events Profile)

This is used as a systematic measure of adverse effects from anti-epileptic drugs (AED). Patients will complete LAEP pre surgery (baseline) and 3 monthly to coincide with clinic visits. Patients may elect to complete paper questionnaires or receive them via an email link for online completion. The patients carer or research assistant (if attending clinic or completing via telephone) may read the questions to the patient or assist with marking the severity number or score as described by the patient. The patient's carer may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report. These reports will be used for descriptive purposes only.

EQ-5D-5L

This is a standardised instrument for use as a measure of health outcome developed by the EuroQoL Group that facilitates the calculation of Quality Adjusted Life Years. It should take approximately 5 minutes to complete. Patients will complete EQ-5D-5L at pre surgery (baseline) and 3 monthly to coincide with clinic visits. Carers will also be asked to complete the Proxy version 1 of the EQ-5D-5L Questionnaire; this asks the carer how they would rate the patients health. The EQ-5D-5L Telephone version will also be collected through a telephone interview with a research nurse when the participant experiences their first episode of seizure like symptoms during the trial period. The patient will continue to complete the questionnaires at the time of clinical and seizure evaluation as long as the patient remains on the study, unless clinical deterioration makes self-reporting not possible before that time. The time when patients are unable to complete the self-report questionnaires will be used as part of the study analysis.

For EQ-5D-5L there will also be an online, face to Face and a telephone version where the carer or Research Nurse can complete on behalf of the patient. In addition, if the patient is unable to communicate their answers, a Proxy 2 version will be available – this is how the carer thinks the patient would rate his/her own health. The Carer will also have the option to complete the Proxy 1 EQ5D-5L online.

Patient Health Questionnaire-9 (PHQ-9)

PHQ9 is a screening tool for depressive symptoms. This instrument is included in recognition of FDA and MHRA advice that AEDs, including levetiracetam, can cause an increased risk of suicidal ideation - although the absolute risk is very low (in licensing studies, prevalence of suicidality on Levetiracetam=0.44%). Prior to randomisation and at the three monthly visits,

patients will complete the PHQ-9 rating scale for depressive symptoms, this will be available on paper, via telephone or an online link sent via email. This widely-used, nine-item rating scale records the patient's report of the frequency of depressive symptoms occurring over the past fortnight. The range of possible PHQ-9 scores is from 0 (no depression) to 27 (highest possible score). The result will be used in ways to promote patient safety on-study.

First, patients scoring ≥20 will be categorised as having 'severe' depressive symptoms. They will be excluded from the study at entry, or during study, and the local clinical team informed. From pilot data in similar populations our starting assumption is that roughly 4% of patients will fall into this category.
Second, all patients will be excluded from the study should they answer >0 to PHQ9 Item 9.
Third, patients who score 15-19 on the PHQ-9 will be notified to their usual clinical team, as having 'moderately severe' depressive symptoms, for them to be aware and assess as they feel appropriate.

The Liverpool Impact of Epilepsy Scale (LIES) and the Liverpool Seizure Severity Score (LSSS)

Patients will be provided with a diary to track any possible seizure events. The Liverpool Impact of Epilepsy Scale (LIES) and the Liverpool Seizure Severity Score (LSSS) will be completed after first seizure and then again one year after randomisation: this is used to assess the impact of epilepsy on a number of different aspects of daily life.

2.6. Cognitive/capacity monitoring

Limited cognitive data that will be gathered for the study, at pre surgery (baseline) and 3 monthly visits –

- Semantic Verbal Fluency Test (SVFT) – a test of Executive Function (taking approximately 1 minute)
- Anterograde Memory test - Recall of a 7 item address after three attempts (taking approximately 2 minutes)
- Documentation on whether the treating clinician considers that the patient has or has not got on-going capacity.

If the clinician considers the patient has lost capacity. We would intend that if the patient has previously agreed that we can gather data in the event they suffer from cognitive decline then data collection would continue (Carer forms and record of first seizure, date, type and severity as determined by the treating clinician / Proxy)

The clinician will stop the study medication if they feel it is no longer safe for the patient to swallow tablets and the date of that decision will be recorded. Should a treatment break be required, e.g. in the event that it is deemed unsafe for the patient to swallow tablets, then standard of care treatment should be followed. This will not form part of the protocol. The clinician should consult with the patient carers and take note of any signs of objection or distress from the participant.

3. TRIAL DESIGN

3.1. General Design

This is a two arm, multicentre phase III randomised trial of prophylactic anti-epileptic drug (Levetiracetam) versus no anti-epileptic drug (AED) (comparator) in patients with suspected cerebral glioma.

Randomly assigned - 1:1 basis

This will not be a blinded study and will not have placebo control and as such will be a "real world" study of prophylactic AED vs. no AED. The reasons for the lack of placebo arm include; real world nature of the study, patient involvement feedback on the design with specific reference to value of a placebo arm; over-encapsulation as levetiracetam capsules are large; and cost of the study.

804 patients will be recruited and randomised into one of two arms:

- **Group 1**: Levetiracetam 500mg twice daily for 2 weeks, then increasing to 750mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500mg prior to surgery. (In those with moderate chronic kidney disease stage 3 estimated Glomerular Filtration Rate (eGFR 30-59 mL/min/1.73 m^2) a starting dose of 250mg twice a day for 2 weeks, then increasing to 500mg twice a day thereafter).

- **Group 2**: no AED treatment (standard care)

3.2. Inclusion Criteria

1) Patients with suspected cerebral glioma on MRI
2) Capable of giving informed consent
3) Patients must be ≥ 16 years old
4) Patients must have a Karnofsky performance status ≥70
5) Patients must be able to safely swallow pills
6) Planned surgery for presumed glioma (biopsy or resection)

3.3. Exclusion Criteria

1) Pregnancy
2) History of any type of seizure for at least 10 years prior to randomisation
3) Known Severe Chronic Kidney Disease (CKD4 - eGFR < 30ml/min)
4) Concomitant methotrexate
5) Concomitant AED (including use for other reasons (e.g. pain))
6) Concomitant benzodiazepines
7) Hypersensitivity to Levetiracetam
8) Active suicidal ideation
9) Any current reported severe depression as defined by a PHQ-9 score of ≥ 20

3.4. Randomisation

After ensuring that the patients meet **all** eligibility criteria and has consented to participate in the study, sites will randomise the patient following the instructions described in the 'SPRING work instructions for sites.

Once a patient has been randomised, a patient study number will be issued and this should be used in all correspondence.

Informed Consent/Authorisation

All Patients that are eligible to receive therapy and randomised to AED arm must undergo an Electrocardiogram (ECG) and pregnancy test (if female and of child bearing age) prior to starting trial medication. AED arm patients must initiate treatment prior to surgery and have taken a minimum of two doses of 500mg Levetiracetam (two doses of 250mg in CKD3 patients) prior to surgery. See Patient Pathway (Page 7).

Prior to protocol enrolment and initiation of treatment, subjects must sign and date an approved consent form.

Eligibility Exceptions

Eligibility exceptions will not be granted.

Withdrawal of Subjects

Patients *discontinue* from the study drug for reasons such as safety or non-compliance. These patients will continue to be followed up for efficacy and safety as per protocol, unless they are lost to follow up or deceased. Patients may *withdraw* from the study at any point and they do not have to give a reason. However, we will ask the patient's permission to continue to collect information on their progress that is routinely recorded in their medical records. This is so that the overall quality of the study is not impaired. The patient can say no at this point and then no further data collection will take place, and will be censored at the point of withdrawal. This should be indicated on the case report form (CRF) as per completion guidelines.

Patients who consent to the trial but do not undergo planned surgery will be withdrawn from the trial. For any patient that did not undergo planned surgery, a further patient would be enrolled to the trial to maintain the target number of patients for analysis.

Please note that should it be medically required, participants in either study arm will be removed from the study and treated with appropriate medication according to standard care.

Patients on the levetiracetam arm who have prolonged QT as detected by pre-surgical ECG and QT interval ≥500milliseconds will not start taking levetiracetam. These patients will ***not*** be withdrawn but, a further patient would be enrolled to the trial to maintain the target number of patients for analysis

Criteria for Removal from Study Drug

- Patient wishes to come off levetiracetam.
- Unacceptable toxicity (as defined in Section 4.4)
- Seizure **(as defined in Section 2.4).** Where patients taking levetiracetam develop a seizure, they will stop taking the study drug and move to a prescribed treatment dose from the treating clinician, this will most likely be maybe a higher dose of levetiracetam. The patient may voluntarily withdraw from treatment at any time for any reason.
- Neurological progression - e.g. development of dysphasia

- Pregnancy (all female patients of child bearing age on the levetiracetam arm will complete pregnancy testing prior to starting trial medication and will complete a pregnancy test at any time the patient confirms there is a possibility of pregnancy)
- Severe depression as defined by a PHQ-9 score of ≥20
- Suicidal ideation on interview.
- Prolonged QT (QT interval ≥500milliseconds) as detected by ECG prior to surgery

NOTE: Unless the treating clinician advises an immediate stop of Levetiracetam for safety reasons, patients will be issued with a taper pack to minimise side effects.

4. TREATMENT

Drug Name: Levetiracetam

Supply: Levetiracetam tablets will be provided in 250 and 500mg strengths from UCB Pharma. Patients will be provided with an initial 4 month supply, followed by a three month supply at each clinic visit.

Dose:
Levetiracetam will be taken orally twice a day at approximately the same times each day, spaced as close to 12 hours apart as possible. Medication may be taken with or without food. Patients with impaired renal function (CKD 3, eGFR 30-59 ml/min/1.73m^2) will have a different dose schedule consistent with the European levetiracetam label. All patients will start on a lower dose for the first 2 weeks and then titrate up as per Table 3 below. The aim of the dose titration is to reduce the side effects experienced by the patients.

Table 3 – Levetiracetam Dose Titration Schedule

Normal treatment	**Impaired Renal Function treatment**
Randomisation-2 weeks 1 tablet of 500 mg AM 1 tablet of 500 mg PM	**Randomisation-2 weeks** 1 tablet of 250 mg AM 1 tablet of 250 mg PM
Next 12 months 1 tablet of 500 mg + 1 tablet of 250 mg = 750 mg AM 1 tablet of 500 mg + 1 tablet of 250 mg = 750 mg PM	**Next 12 months** 1 tablet of 500 mg AM 1 tablet of 500 mg PM

Dose Reduction/Tapering:
Any patient reporting side effects from levetiracetam will be recorded and reported as per the Safety reporting section (section 5). Doses between 250mg bid or 750mg bid are permissible during the study. However, every effort should be made to maintain the target dose whenever possible. The treatment may be suspended, at the discretion of the treating investigator, however continuing therapy at a reduced dose should be seriously considered because of the risk of seizure associated with sudden cessation of any AED.

Once the patient has completed the trial at 12 months the hospital consultant/GP may recommend that the patient continues on this medication and if so they can arrange for it to be supplied on a prescription. All other patients should receive a dose reduction pack and the dose should be tapered according to Table 4 below:

Table 4 – Levetiracetam Dose Tapering Schedule

Normal treatment	Impaired Renal Function treatment
Week 1 1 tablet of 500 mg + 1 tablet of 250 mg = 750mg AM 1 tablet of 500 mg = 500 mg PM	***Week 1*** 1 tablet of 500 mg = 500 mg AM 1 tablet of 250 mg = 250 mg PM
Week 2 1 tablet of 500 mg = 500 mg AM 1 tablet of 500 mg = 500 mg PM	***Week 2*** 1 tablet of 250 mg = 250 mg AM 1 tablet of 250 mg = 250 mg PM
Week 3 1 tablet of 500 mg = 500 mg AM 1 tablet of 250 mg = 250 mg PM	***Week 3*** 1 tablet of 250 mg = 250 mg AM
Week 4 1 tablet of 250 mg = 250 mg AM 1 tablet of 250 mg = 250 mg PM	*No further treatment*
Week 5 1 tablet of 250 mg = 250 mg AM	*No further treatment*
Week 6 *No further treatment*	*No further treatment*

4.1. Pre-treatment Evaluation

General Requirements

1) A history and neurological examination (to include demographic information and documentation of the Karnofsky Performance Status and Semantic Verbal Fluency Test (SVFT) shall be performed on all patients.
2) Documentation of tumour diagnosis on CT/MRI.
3) Blood test to confirm kidney function within the prior month as per routine pre-surgical blood screening
4) Patients will complete the pre surgery (baseline) assessments prior to the first dose of study medication at the clinic. At this time the assessments (PHQ-9, LAEP and EQ5D-5L) will be completed, by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the carer or research nurse may read the questions to the patient or assist with marking the severity number or score as described by the patient. Proxy versions of EQ-5D-5L will also be available. Carers will also be asked to complete the Proxy version 1 of the EQ-5D-5L Questionnaire, this asks the carer how they would rate the patients health.

4.2. Treatment Schedule

Due to the nature of the trial, patients may present in two categories, those requiring urgent surgery (admitted to hospital, surgery within approximately 7 days) and those who will be outpatients awaiting an elective surgery date.

Outpatients may be seen prior to their pre-surgical visit, therefore the trial may be discussed with them during these appointments. If the treating clinician will not see the patient at a face-to-face visit, but instead have a telephone/video interview, prior to the pre-surgical visit, the patient informed consent may be posted to the patient to allow the patient additional time to consider participation. The full informed consent will be completed at the pre-surgical visit. The patients randomised to the levetiracetam arm will also leave the appointment with their initial levetiracetam supply to allow them to start the prophylactic treatment prior to surgery.

Inpatients may be in the position of requiring urgent surgery, the consent and randomisation may have to take place in a short period of time. Prior to randomisation, the trial team must ensure the patient has a minimum of 12 hours prior to surgery to allow for 2 doses of levetiracetam. Care will be taken by the trial team to allow for as much consideration time as possible prior to randomisation. If the patient does not feel able to make a decision with the time available to them they will be excluded from the trial.

Female patients of child bearing age randomised to the levetiracetam arm will be asked to complete pregnancy testing prior to starting medication. If they are pregnant, the patients will be withdrawn from IMP as per section 3.4.

Any patients randomised to the levetiracetam arm will receive an ECG prior to starting medication. Any patients who have prolonged QT as detected by pre-surgical ECG and QT interval ≥500milliseconds will not start taking levetiracetam as per section 3.4.

All patients will be monitored for clinical evidence of toxicity as described below

Unless otherwise noted, all evaluations may be performed within 14 days before the next scheduled clinic date.

1) All relevant information regarding drugs, doses, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and flow sheets.

2) A history and neurological exam (to include documentation of the patient's Karnofsky Performance Status, Semantic Verbal Fluency Test (SVFT)) and an Anterograde Memory test (Recall of a 7 item address after three attempts) will be performed at least every 3 months, +/-2 weeks.

3) All patients will be followed for overall survival. Patients will be seen at 3 monthly clinic visits. In addition, all patient reported events will be recorded and safety reporting completed if required (Safety reporting detailed in section 5).

If patients have a seizure they will complete:

- Patient diary
- The Liverpool Impact of Epilepsy Scale (LIES) after first seizure then again one year after randomisation: this is used to assess the impact of epilepsy on a number of different aspects of daily life.
- The Liverpool Seizure Severity Scale (LSSS) will be completed after first seizure and again one year after randomisation.

The EQ5D-5L will be completed after first seizure.

4.3. Visit Schedule

Patient Visit Schedule

	Screening / pre-surgery	Post-surgery	3 month (+/- 2 wks)	6, 9, 12 month (+/- 2 wks)	18 month [a] (+/- 2 wks)	Reported suspected seizure
Written informed consent	X					
Demographic data	X					
Medical /seizure history	X		X	X		
Concomitant medications	X		X	X	**S** - details of AEDs only	
PHQ9	X		X	X		
Karnofsky Performance Status (Neurological exam)	X		X	X		
Semantic Verbal Fluency Test (SVFT) (Neurological exam)	X		X	X		
Anterograde Memory test (Neurological exam)	X		X	X		
Tissue	**S**					
Blood (eGFR -kidney function)	**S**		**S**	**S**		
ECG[d]	X					
Pregnancy testing[c]	X					
Standard MRI imaging	**S**	**S**	**S**			
Liverpool Adverse Events Profile	X		X	X		
EQ-5D-5L	X		X	X		X
Carer EQ-5D-5L	X		X	X		
Liverpool Impact of Epilepsy Scale						X
Liverpool Seizure Severity Scale						X
Health Economic Questionnaire	X		X	X		
Time & Travel Questionnaire[b]				X		

Key: X – Completed as Trial activity **S –** Standard of care, to be completed as per institution guidelines **S -** Standard of care, to be completed as per institution guidelines, 3 month MRI will capture institution MRI between post-surgery and up to 6 months.

[a]Follow up will be every 3 months to at least one year after randomisation, where possible 18 month data will be collected until the end of trial [b]Time and Travel Questionnaire is at 6 month visit only [c] Pregnancy test should take place before first dose of IMP (if on IMP arm) [d]ECG before first dose of IMP (if on IMP arm)

4.4. Treatment Breaks

- A 'treatment break' is a planned interruption to taking the study drug. If the treatment break is related to surgery, for example if the patient is admitted to a high dependency unit following surgery and unable to swallow the study drug then a treatment break of ≤14 days is permitted. The patient should then recommence study treatment at the prior treatment dose (starting dose) and escalate after that dose finishes. A scenario could be if the patient on the treatment arm is taking study drug for 4 days, then has a treatment break of 4 days post surgery, they will recommence on the starting dose for a further 10 days before escalating to the next dose. During a treatment break, standard of care treatment should be followed. This will not form part of the protocol. Following the recommencement of study drug the initial treatment dose would continue until 14 days of the study drug is given before escalation to the next dose.

- The clinician will be able to stop the study medication if they feel it is no longer safe for the patient to take tablets and the date of that decision will be recorded. In this instance, standard of care treatment should be followed. This will not form part of the protocol.

- Any treatment breaks should be recorded on the appropriate eCRF page.

4.5. Concomitant Therapy

Anti-tumour Treatment:

- Standard and experimental anti-tumour therapies are permitted.

Supportive Care:

- Dexamethasone should be used in the smallest dose to control symptoms of cerebral oedema and mass effect, and discontinued if possible.

- Febrile neutropenia may be managed according to the local institution's Infectious Disease guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.

- The use of anti-emetics will be left to the investigators' discretion.

- Methotrexate use is an exclusion criteria and as such methotrexate should not be prescribed to patients enrolled in this trial. Where it is considered necessary to prescribe methotrexate patients should be removed from the trial.

- Therapies considered necessary for the wellbeing of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except

for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

4.6. Drug Supplies and Labelling

The investigational product will be supplied by UCB Biopharma in blister packs. The investigational medicinal product (IMP) will be labelled and boxed and distributed to site for dispensing by site pharmacies. The patients will be provided with an initial 4 month supply at the Pre surgery (Baseline) visit followed by a three month supply at each scheduled clinic visit.

Details relating to IMP ordering and distribution can be found in the SPRING work instructions for sites.

4.7. Drug Storage and Accountability

Storage
All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational labels. Study treatment must be kept out of the reach and sight of children.

Accountability
The investigator or a delegated individual (e.g. pharmacist) must ensure that the study drug is stored and dispensed in accordance with hospital standard operating procedures and applicable regulatory requirements.

The medication provided for this study is for use only as directed in the protocol. Drug distribution and accountability logs will be provided to the site in a pharmacy pack. It is the investigator's responsibility to establish a system for handling the investigational product to ensure that:

- Deliveries of investigational products are correctly received by a responsible person (e.g., pharmacist or suitable pharmacy designee) and are handled and stored correctly and safely
- Investigational products are dispensed only in accordance with the protocol
- Participants return any unused investigational product to the investigator at the end of the trial
- A dispensing record (which will include the identification of the participant to whom the investigational product was dispensed, the date of dispensing, the quantity of investigational product dispensed, and the date and quantity of any unused investigational product returned to the pharmacy) is accurately maintained. Any discrepancies must be accounted for on the appropriate form.

In the case that any study drug is damaged, please contact SCTRU for reconciliation and replacement.

At the termination of the study or at the request of the sponsor, all unused drugs will be accounted for and destroyed locally at the study sites. Certificates of delivery and destruction or return must be signed and copies retained in the Investigator Site File.

Accountability records must be completed and any study drug remaining at the end of the trial must be destroyed according to the sites local standard procedures.

5. PHARMACOVIGILANCE

5.1. Definitions

Adverse Reaction (AR): All noxious and unintended responses related to a study treatment or procedure should be considered adverse drug reactions.

Serious Adverse Event (SAE): Any untoward medical occurrence in a patient that

a) Results in death
b) Is life-threatening
c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability or incapacity
e) Consists of a congenital anomaly or birth defect
f) Is otherwise considered to be medically significant by the investigator (e.g. intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias).

The term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisations planned prior to enrolment in the trial or for social reasons should not normally be considered as SAEs unless the hospitalisation has to be prolonged. Treatment in an emergency room of less than 24 hours or on an out-patient basis that does not meet any other serious criteria should not be considered as an SAE.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is classified as serious and it is thought to be caused by a study treatment or procedure. Expected events are detailed within the Summary of Product Characteristics (SmPC). The nature, severity or outcome of this adverse reaction must not be consistent with SmPC for the treatment or procedure.

5.2. Emerging safety profile

Levetiracetam is approved for the treatment of patients with newly diagnosed epilepsy. The SPRING trial will use levetiracetam out with this indication to investigate prophylactic use.

This Summary of Product Characteristics (SmPC) lists those events that are to be regarded as expected for regulatory reporting purposes (please refer to the SmPC for any updates).
https://www.medicines.org.uk/emc/product/2294/smpc
https://www.medicines.org.uk/emc/product/2293/smpc

5.3. Recording and Reporting of Adverse Reactions

All related Adverse Reactions will be recorded in the Case Report Form and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5. Any Adverse Reaction considered unrelated will not be recorded.

All adverse reactions that occur after the signing of written informed consent and within 30 days after the final study treatment will be recorded on the appropriate eCRF page. The exception to this would be any event occurring after signing the informed consent and prior to commencing study treatment that is considered unrelated to trial procedures. In addition, any events occurring more than 30 days after final study treatment that are deemed to be related to the study drug should be notified to PHS as detailed in section 5.4.

5.4. Modified Safety Reporting

The events listed below are expected within the study population and will be exempted from routine SAE reporting, however they will be assessed for relatedness to the study drug and if the event is considered related to study treatment and not expected *i.e.* it is a SUSAR it will be reported in an expedited manner. In addition, a quarterly line listing of these events will be reviewed by the Chief Investigator and sponsor.

- Any Seizure
- Reported changes in memory, mood, personality and fatigue
- Progressive neurological deficit
- Death due to disease progression
- Elective hospitalisation and surgery for treatment of brain cancer or its complications.
- Elective hospitalisation to make treatment or procedures easier.
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.

5.5. Recording and Reporting of Serious Adverse Events

All serious adverse events (not subject to modified safety reporting in section 5.4) that occur after the signing of written informed consent and within 30 days after the final study treatment will be recorded on the SAE report form. Study treatment should be considered any study

activity from informed consent until the final follow up visit or end of final medication (if on IMP arm and in receipt of taper pack). The CTCAE grading will also be captured.

The exception to this would be any event occurring after signing the informed consent and prior to commencing study activity that is considered unrelated to trial procedures. In addition, for patients on IMP arm any events occurring more than 30 days after final study treatment that are deemed to be related to the study drug should be notified to PHS as above.

The SAE case report form must be completed on the Trial eCRF and signed by the Principal Investigator of the centre involved within 24 hours of first becoming aware of the event.

All initial SAE reports should contain the following minimum information:

- Reporter information
- At least one subject identifier (trial number/patient initials)
- Event term
- Assessment of relatedness
- Suspect drug or procedure
- Serious criteria

Sites should email phs.sctru@nhs.net to notify PHS that an SAE has been reported.

All SAEs for patients on the IMP arm will be forwarded to the CI by PHS for assessment of expectedness against the SmPC. Any SAE that is deemed to be both related and unexpected (i.e. a SUSAR) will be notified to the appropriate Competent Authorities and Research Ethics Committee within 7 days of becoming aware of the event for fatal or life threatening events and 15 days for all other serious events.

Hospitalisations planned prior to enrolment in the trial should not normally be considered as SAEs unless the hospitalisation has to be prolonged. Treatment in an emergency room of less than 24 hours or on an out-patient basis that does not meet any other serious criteria should not be considered as an SAE.

Please refer to SPRING instruction manual for sites for reporting instructions.

5.6. Developmental Safety Update Report

A developmental safety update report will be submitted to the appropriate Competent Authorities and Research Ethics Committee, once a year for the duration of the trial. The time frame for the report starts with the date of first authorisation by a competent authority in an EU member state and the report should be submitted within 60 days of the anniversary of first authorisation.

5.7. Pregnancies

Pregnancy is an exclusion criterion for enrolment and patients of child-bearing age (pre-menopausal female capable of becoming pregnant) will take a pregnancy test if randomised to the levetiracetam arm.

All female patients of child-bearing age will be advised to use contraception throughout the trial. There are no known contraceptive drugs which are contraindicated while taking levetiracetam.

Acceptable methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Barrier method – Condom, with or without spermicide
- Barrier method – Cap, must be used with spermicide

Any female patients of child bearing age randomised to the levetiracetam arm will be asked to contact their local site immediately, should there be any possibility they have become pregnant. The local site will arrange for a face-to-face visit as soon as possible and for the patient to have a urine pregnancy test and if positive, the study drug will be stopped and reasons given. Should the patient have had seizures, the decision whether or not to alter drug dose for seizure management will be the decision of the treating doctor.

During the follow up visits, whether face-to-face or telephone/video-call, any female patients of child bearing age randomised to the levetiracetam will be asked to confirm if there is any chance they have become pregnant since their previous visit. If there is any possibility the site will arrange for a urine pregnancy test. If the follow up visit is to be by telephone / video interview, the patient will be asked to attend their site. As above, if the test is positive, the study

drug will be stopped if the patient has been seizure free and reasons given. If seizures have occurred, the seizure management will be the decision of the treating doctor.

Any female patient who reports a pregnancy while on the trial will be followed up to determine outcome, including spontaneous or voluntary abortion, details of birth and presence or absence of any birth defects, congenital abnormalities or maternal or newborn complications. Any birth defects or congenital abnormalities must be reported as SAEs.

Pregnancy should be reported to PHS within 24 hours of becoming aware by completing the pregnancy case report form on the electronic data capture system. An email should be sent to phs.sctru@phs.scot to notify PHS that a pregnancy has occurred.

6. DATA MANAGEMENT

All data will be handled, computerised and stored in accordance with the Data Protection legislation and Public Health Scotland Confidentiality Guidelines.

6.1. Data Collection

Data generated will be entered by site staff onto a Trial specific eCRF. SCTRU will be responsible for checking the data, and validating it. All source data should be recorded within patient files.

The data collected will include:

- initial clinical details at randomisation
- drug administration (CTIMPs)
- adverse events
- survival/ recurrence details
- patient questionnaires

During the SPRING trial the Covid-19 pandemic has led to lockdown and patient shielding. As such, data regarding suspected Covid-19 illness dates and Covid-19 test results will be gathered.

6.2. Record Keeping and Archiving

PHS will store study documentation until the end of patient follow up. The documentation will then be archived according to current legislative requirements.

6.3 Data Security

The Trial eCRF system will be hosted by Elsevier Macro with full systems administration to allow user role management. Remote access requires a 128-bit encrypted password rdp connection. The system has a full audit trail and system log to track user activities. Elsevier security measures include managed gateway firewalls, anti-virus protection, and data back up

using dedicated data protection software. The Elsevier data centre is ISO 27001 Information Security Management certified.

In the event of a data security breach, SCTRU will follow the Public Health Scotland (PHS) Information Governance, Information security, and Adverse event management policies.

Patient and Carer questionnaires will be accessed via REDCap if patients or carers elect to use this option. REDCap is a data neutral secure web application for building and managing online surveys and databases and is compliant with 21 CFR Part 11, FISMA, HIPAA, and GDPR.

7. STATISTICS

7.1. Sample Size

Estimate of 1 year seizure rate in patients with suspected cerebral glioma after surgery is 20%. We anticipate a reduction in seizure rate to 10% in the treatment arm. Based on a 90% power to identify an improvement in 1 year seizure rate in the treatment arm compared to the control arm, this requires 532 patients across the two arms with a two-sided type I error level of 5%. Assuming a 24.8% 1 year mortality rate and that 12% of patients will be lost to follow-up, the final (maximum) sample size is 402 per arm.

Patients will be randomly assigned at a 1:1 ratio to the following groups:

- **Group 1**: Levetiracetam 500mg twice daily for 2 weeks, then increasing to 750mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500mg prior to surgery. In those with moderate chronic kidney disease (eGFR 30-59 mL/min/1.73

  m2) a starting dose of one 250mg twice a day for 2 weeks, then increasing to 500mg twice a day thereafter).

- **Group 2**: no AED treatment (standard care)

We anticipate an initial 6 month start up period, recruitment over 3 years, 1 year follow-up period and a further 9 months for data cleaning, analysis and report writing (total 65 months).

Conservative estimate of 1 year seizure rate in patients with suspected cerebral glioma after surgery is 20%. Based on the effect of levetiracetam of reducing seizure in patients with epilepsy we anticipate a reduction in seizure frequency to 10% in group 1.

Attrition due to limited Life Expectancy

The proportion of expected participants have been taken from the recognised potential frequency of cerebral glioma (low grade (Grade 1-2)/ high grade (Grade 3-4)[11-14]. There will be a smaller proportion of high-grade cerebral glioma, as a higher proportion of grade 4 (Glioblastoma Multiforme) have a poorer performance status, which may preclude entry into

the study. However, more cases with grade 1 and grade 2 tumours will present with seizures, therefore will not be suitable for this study. On balance, we think that the proportion of cases with each grade are justifiable and are likely to represent the proportion recruited who would be at risk of first seizure.

The median survival statistics and mortality by 1 year for each grade of cerebral glioma (Grade 2-4) have been taken from routine "standard of care" randomised control trial papers for treatment: Grade 4[11-14]. There are no suitable trials in grade 1 cerebral glioma, but we anticipate there will be relatively few of these and therefore have included the percentage number of cases in with the frequency of grade 2 tumours (Table 5).

Table 5:

Tumour Type	Proportion of study population	Median Survival(months)	Mortality by 1 year	Mortality as a % of population	Attrition due to mortality
Grade 4 (GBM)	65%	14.6	38.4%	25.0%	22.2%
Grade 3	20%	39/57	10.0%	2.0%	1.8%
Grade 2	15%	84	6.8%	1.0%	0.9%
Total	100%			28.0%	24.8%

We have estimated an attrition rate in this population of 24.8% due to mortality at 1 year

Attrition Rate drop-out due to Adverse Events

In general in epilepsy studies, treatment failure for unacceptable side-effects is largely limited to the early post-randomisation period. We wish to gain the earliest effect, because of the risk of early seizures (up to 5% in first post-operative week) in cerebral glioma patients, but appreciate that early attrition could be a problem if there was drop out due to intolerable side effects. It is recognised that levetiracetam has fewer early adverse events due to rash or haematological toxicity and drug-drug interactions than first generation AEDs (phenytoin, carbamazepine) and lamotrigine.

In a systematic review of the literature around levetiracetam dose and drop outs from study - we have looked at:

a) Dropout rates in RCT of levetiracetam vs. Carbamazepine for non-tumoural resistant epilepsy. (Staring dose 500mg bid – and increased as necessary to 1.5gr bid). Withdrawal rates were 14.4% with levetiracetam and 19.2% with carbamazepine[5].
b) Dropout rate in RCT of intravenous levetiracetam vs. Phenytoin for prophylactic seizures after craniotomy) - (levetiracetam 11% vs. Phenytoin 13% at 3months)[6].
c) Dropout rate in RCT of levetiracetam vs. Phenytoin post-operatively in cerebral glioma patients who had previously had a seizure pre-operatively. (Starting dose oral 1 gram bid and altered accordingly). Levetiracetam had fewer side effects at 3 and 6 months and there were no drop-outs because of side effects at 6 months. 73% of patients taking

levetiracetam remained on the initial dose of 1,000 mg bid. (21% reduced their dosage to 500 mg bid, and 6% increased to a higher dose 1,500 mg bid because of seizure)[25].

The maximum dosage of levetiracetam used in SPRING will be 750mg bid. This is the World Health Organisation defined daily dose and is only 50% of the maximum recommended dose for resistant epilepsy.

We have estimated a dropout rate in this population of 12% due to intolerable side effects.

In the literature, a conservative estimate of frequency of seizures in the first year following surgery in cerebral glioma is >20%. Anti-epileptic drugs are effective at controlling tumour-associated epilepsy in 50% and reduce severity in 20-30%. Levetiracetam has a good side effect profile, but we have estimated a discontinuation rate of 12%. Cerebral cerebral gliomas are life limiting and we have estimated the attrition due to death from the disease at 24.8%.

Sample size was calculated to provide a 90% power to identify an improvement in 1 year seizure rate in the treatment arm compared to the control arm with a two-sided type I error level of 5%. This results in a requirement of 80 seizures (events) during the trial. Assuming a 24.8% 1 year mortality rate and that 12% of patients will be lost to follow-up the final (maximum) sample size is 804 (402 in each arm).

This is a two-arm phase III trial (90% power (1-β), 5% (α) 2-sided significance level) with a randomisation ratio of 1:1 (1:φ).

We use the odds ratio of the treatment arm and control as the primary outcome measure. The odds ratio is defined as the ratio of the odds of seizure in the treated group divided by the odds of seizure in the untreated group.

We assume the following 1 year seizure avoidance rates for the study arms

λ_0 = 0.80 for control arm i.e. 20% seizure rate

λ_1 = 0.90 for treatment arm (750mg BID) i.e.10% seizure rate

With a sample size of 532 this gives the following number of seizures in each study arm:

	No AED	Levetiracetam
Seizure within 1 year	53.2 (a)	26.6 (b)
No seizure within 1 year	212.8 (c)	239.4 (d)

The odds ratio can then be found as follows:

OR = (a x d)/(b x c) = 2.25

From this we can see that the number of seizures required is a + b = 79.8 (rounded to 80).

If we experience a 1 year mortality of 24.8% and attrition through intolerable side-effects in 12% of patients then $N_{adjusted}$ = 532/((1-0.248)*(1-0.12) = 803.9 patients (rounded to 804). Therefore each arm should recruit 402 patients.

Recruitment Rate:
Estimates of number of patients that can be recruited from pilot sites, based on cases in each of the four centres over the last years, and a 50% recruitment rate, suggest that the study would be able to recruit over 989 patients over a 3 year period (see table 6 below).

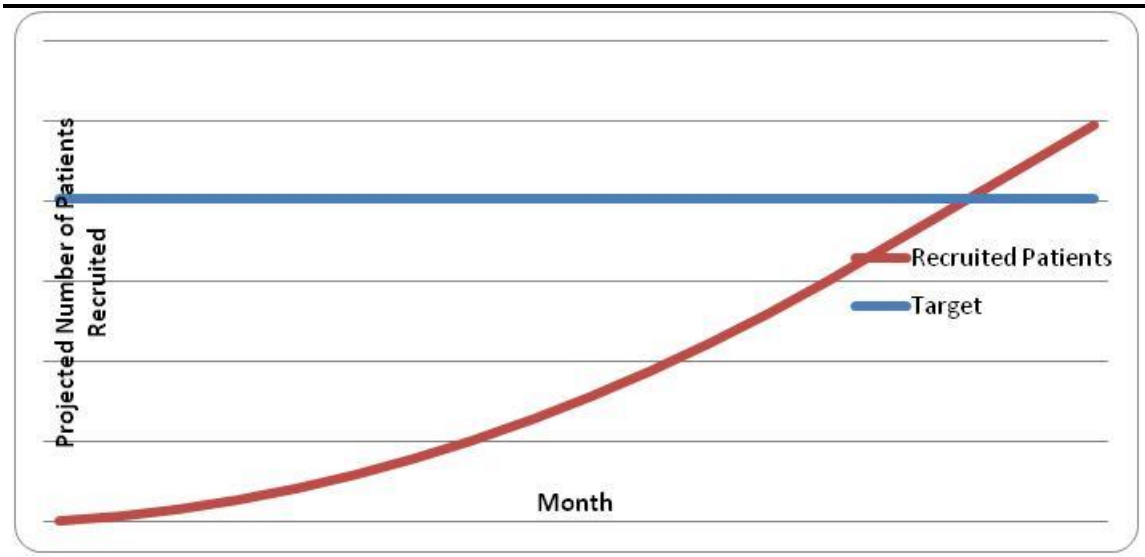
Table 6: Recruitment Rate

	Estimate of patients recruited per month	Total for study (3 years)*
Liverpool	4.25	153
Edinburgh	2	70
Cambridge	4.25	140
King's college	1	31
Total for 4 sites	11.5	394
Average for 4 sites	2.875	98.5
Total for 11 additional sites (if similar to average of 4 sites above)	31.625	595
Total for 15 sites	43.125	989

(*These figures allow for a lag in opening site with sites opening in months 1,2,4,6,8,10,12,14,16,18,20,22,24,26 and 28.)

The figure below shows the recruitment figures projected for the full period of the study (36 months). This projection suggests that we could meet our recruitment target of 804 patients at month 32.

Figure 1: Projected number of patients recruited over the study period.



7.2 Randomisation and Stratification

This is a multicentre, randomisation study and a centralised registration system will be used to assign patients to treatment groups (1:1 allocation; 402 patients in each group). Patients will be allocated to treatments using a minimisation algorithm. The factors used in the algorithm will be:

- High grade vs. Low Grade
- Treatment Centre
- Type of surgery intended

7.3 Analysis Plan

The primary analysis will be performed on the intention-to treat population. A full statistical analysis plan will be developed prior to any analysis being performed.

7.3.1 Primary Efficacy Analysis

The primary analysis will be performed on the intention to treat population. A full statistical analysis plan will be developed prior to any analysis being performed.

One year occurrence of seizure

The occurrence of seizures within one year of randomisation will be compared between the study arms. The odds ratio, associated 95% confidence intervals and 2-sided p-values associated with the comparison of the arm from a logistic regression model fitted to the

presence of a seizure within one year of randomisation will be given. The estimated absolute difference in seizure rate will be reported together with associated 95% confidence interval.

This is the primary comparison.

7.3.2 Secondary Efficacy Analysis

The secondary study measures are:

- Time to first seizure
  The time to first seizure, within one year of randomisation, will be compared between the study arms using an accelerated failure time model. The acceleration factor and 2-sided p-values associated with the comparison of the two study arms from the accelerated failure time model fitted to the timing of a seizure within one year of randomisation will be given.

- Time to first tonic clonic seizure
  The time to first tonic clonic seizure, within one year of randomisation, will be compared between the study arms using an accelerated failure time model. The acceleration factor and 2-sided p-values associated with the comparison of the two study arms from the accelerated failure time model fitted to the timing of a seizure within one year of randomisation will be given.

- Patient reported symptoms and adverse events
  Adverse events will be graded in accordance with CTCAE v5.0. The grade of the tabulated adverse events will be compared between the study arms using a Mann-Whitney U test (exact method).

- Mood, personality, fatigue and memory
  Mood, personality, fatigue and memory will be assessed through the Liverpool Adverse Events Profile (LAEP) questionnaire. Additionally depressive symptoms will be assessed in detail using the PHQ-9 data. The grade or prevalence of these symptoms will be compared between study arms using a Mann-Whitney U test (exact method).

- Progression Free Survival
  Progression will be determined clinically based upon interpretation of MRI scans, clinical state of the patient and steroid dose. Where an MRI is used to determine progression the date of progression will be the date of the scan. If steroid dose is the primary factor in determining progression the date of progression will be the date the dose was started or increased. Where clinical state is used to determine progression the date of progression will be the date of assessment.

  Progression free survival will be calculated as the difference between date of progression and date of randomisation.

  A Kaplan-Meier plot of progression free survival will be presented. The median progression free survival time for each study arm will be tabulated together with the

  corresponding 80% confidence interval. The corresponding hazard ratio and 80% confidence interval and 2-sided p-value associated with the comparison of the treatment arms from the Cox model fitted to the data will be reported.

- Overall Survival
  A Kaplan-Meier plot of overall survival will be presented. The median overall survival time for each study arm will be tabulated together with the corresponding 80% confidence interval. The corresponding hazard ratio and 80% confidence interval and 2-sided p-value associated with the comparison of the treatment arms from the Cox model fitted to the data will be reported.

- Quality adjusted life years
  Once QALYs have been calculated, these values will be presented for the two randomised group, as well as QALYs calculated with the incremental cost per QALY gained at 12 months. As the trial follow up period is 12 months, costs and effects will not be discounted.

  These data will be analysed using both the trial data (unadjusted costs and effects) and regression analyses, specifically seemingly unrelated regression models [40], which can simultaneously estimate both costs and health outcomes at the individual level whilst taking into account the fact that the contemporaneous error terms may be correlated. Statistical imprecision will be presented as confidence intervals around differences in effectiveness, cost and cost-effectiveness.

- Cost to the NHS and personal social services
  Once mean costs have been calculated, these values will be presented for the two randomised group, as well as incremental mean costs calculated with the incremental cost per QALY gained at 12 months. As the trial follow up period is 12 months, costs and effects will not be discounted.
  A within-trial economic analysis will estimate the incremental cost per quality adjusted life year (QALY) gained over a 12 month time horizon. The perspective of the analysis (i.e. whose costs and benefits are considered) will be the NHS and personal social services, but we will also take a wider perspective by including costs borne by trial participants, for example out of pocket expenses on health care and the time and travel costs of accessing care.

- Model costs, QALYs & incremental cost per QALY gained
  The output of the economic model will be used to produce estimates of costs, effects, incremental costs, QALYs, and ultimately measure cost-utility. Cost-effectiveness will be reported as incremental cost per QALY gained over the patient's lifetime. As the duration of the model-based analysis is greater than one year, both costs and effects will be discounted at 3.5% in the base case analysis where appropriate, in line with current guidance from NICE [41].

  To explore uncertainty in the model parameters such as variations in unit prices, and parameter statistical imprecision we will conduct extensive deterministic (e.g. for unit prices) and probabilistic (for statistical imprecision) sensitivity analyses. For the latter we will attach appropriate distributions to the model input parameters. This method

requires treating each input in the model as a distribution and using Monte Carlo simulation. The results from this analysis will be presented as plots of costs and QALYs derived from the probabilistic analysis and Cost-Effectiveness Analysis Curves.

7.3.3 Interim Analyses

An interim analysis will be performed at the end of the internal pilot period (12 months after first site opened). The aim of the analysis is to establish that recruitment in to the study is achievable within time frames specified. The following stop/go criteria will be used:

A) Site initiation

1) If 4 or more sites are open and have recruited at least one patient per site, proceed to main trial.

2) If 2 or 3 sites are open and have recruited at least one patient per site, consider procedure for identifying and opening trial sites and identify aspect amenable to change. Then proceed to main trial.

3) If less than 2 sites are open and have recruited at least one patient per site, and no obvious solution exists, abandon the plan for the main trial.

B) Consent rate

1) If the consent rate is 50% or higher, proceed to the main trial.

2) If the consent rate is between 30% and 50%, consider information collected on the reasons why patients do not want to participate and identify aspects amenable to change. Then proceed to the main trial as amended.

3) If the consent rate is less than 30% and no obvious solutions exist to increase this, abandon the plan for the main trial.

C) Recruitment

1) If 125 or more patients are recruited into the trial, proceed to main trial.

2) If between 80 and 125 patients are recruited into the trial, consider information collected on the screening logs to identify why clinicians are not considering patients for the study and identify aspects amenable to change. Then proceed to main trial.

3) If less than 80 patients are recruited into the trial and no obvious solutions exist to increase this, abandon the trial.

D) Loss to follow up

1) If loss to follow up occurs in no more than 10% of patients, proceed to the main trial.

2) If loss to follow up occurs in between 10% and 30% of patients then use the information captured on reasons for losses to follow up and identify any aspects amenable to change. Then proceed to the main trial as amended.

3) If loss to follow up occurs in more than 30% of patients and no obvious solutions exist, abandon the plan for the main trial.

E) Toxicities

1) If withdrawal due to intolerable toxicity within 4 weeks of starting treatment occurs in no more than 10% of patients, proceed to trial.

2) If withdrawal due to intolerable toxicity within 4 weeks of starting treatment occurs in more than 10% and less than 20% of patients, review starting dose and titration policy.

3) If withdrawal due to intolerable toxicity within 4 weeks of starting treatment occurs in more than 20% of patients, abandon trial.

An interim analysis of the health economics component of the study will also be performed at the end of the internal pilot period. The aim of this analysis is to ensure that the data collection tools are appropriate for the full trial. The focus of this interim analysis will be on the cost questionnaires. The health economists will monitor competition rates, summarise the data that has been collected, and identify areas in which the questionnaires could be improved in the full trial to reduce the burden on the trial participants and increase the quality of data collected.

Notes
All above criteria will be assessed at the end of the pilot study. These criteria will be reviewed within one month following the end of the pilot study. During this time, recruitment will continue.

Throughout the pilot study the SPRING study team will conduct frequent data prompts to ensure the data is as up to date as possible when reviewing the above criteria.

If any of the criteria within this pilot are not met then plans on how to revise the trial will be submitted to the DMC and TSC prior to discussions with the trial funders. In particular, during the internal pilot, screening logs at all sites will be kept and the information used to inform decisions on whether to amend or close.

7.3.4 Final Analysis

The Final Analysis will take place when all patients have been followed up for a minimum of one year following randomisation.

7.3.5 Health Economics

The health economic component of this study will consist of three main stages:

1) A within-trial analysis
2) An assessment of utility associated with seizures
3) A Model based analysis

1) Within-trial economic analysis

In order to estimate the cost-effectiveness of levetiracetam prophylaxis compared to usual care (no levetiracetam prophylaxis) in the trial period, a within-trial economic analysis will estimate the incremental cost per quality adjusted life year (QALY) gained over a 12 month time horizon. The perspective of the analysis (i.e. whose costs and benefits are considered) will be the NHS and personal social services, but we will also take a wider perspective by including costs borne by trial participants, for example out of pocket expenses on health care and the time and travel costs of accessing care.

Estimation of NHS resource use and costs

Intervention costs will be based upon the costs of the randomised interventions received, and will be micro costed. This will include costs of medications, on-going monitoring (including equipment costs and staff costs), and managing any adverse events (AEs) that may occur. The use of services for the initial treatment (including time in hospital) will be collected through case report forms (CRF). The CRFs will be tailored to reflect the needs of the study participants and to ensure that there is no double counting of the use of services. The CRFs will also collect data on the use of other secondary care services, for example the duration of any hospitalisations, the number of outpatient visits, use of tests and changes in medications. We will also explore the opportunity to elicit the use of secondary care services from routine data sources such as NHS Digital, and should this be possible we will use this in preference to using information collected from the CRF, resulting in the CRF being shortened and simplified.

Use of primary care will be collected via questionnaire administered at clinic visits at pre surgery (baseline), 3 months, 6 months, 9 months and 12 months post randomisation. This questionnaire will be completed by the trial participant themselves in the first instance, however if it is felt necessary, a carer will assist the trial participant in completing the questionnaire. The questionnaire will also capture out of pocket expenses such as purchase of health care. Costs

for health care services will be obtained from standard sources such as NHS reference Health Resource Group tariffs [42] the British National Formulary for medications [43]. Further data will come from the study centres themselves, for example the costs of consumables and other equipment used in the surgery. The price year adopted for the base case analysis will be the year when the final analysis is conducted. For each participant, measures of the use of resources will be combined with unit costs to provide a cost for that participant.

Estimation of costs falling on patients and their families

The participant completed questionnaire completed at pre surgery (baseline), 3 months, 6 months, 9 months and 12 months post randomisation will also capture out of pocket expenses such as purchase of health care. Where possible the use of these privately purchase services will be valued using the actual purchase price paid by the participant or where that is not available imputed from analogous sources e.g. The Unit cost of Health and Social Care for contacts with primary care [44].

Further patient costs (the time and travel costs for accessing particular types of care) will be based upon a time and travel questionnaire adapted from one developed by the UK working group of patient costs and successfully used in a large number of NIHR HTA programme funded projects previously [45]. This questionnaire will be given to the trial participant at the 6 month visit, together with a stamped addressed envelope. The participant will be asked to complete the questionnaire at home, before posting it back to the trial office. The responses from this questionnaire will then be used to estimate the unit cost of accessing each type of care. For each participant, measures of the use of services collected via the CRF and the participant completed questionnaire will be combined with unit costs to provide a total cost for that participant.

Estimation of Quality-adjusted life years (QALYs)

The relative changes in health related quality of life (HRQoL) resulting from the physical and psychological benefit together with any harms associated with each treatment strategy will be based upon responses to the EQ-5D-5L, which will be administered face to face at pre surgery (baseline), 3 months, 6 months, 9 months and 12 months post randomisation. The Proxy 1 version will also be completed by the patients Carer if possible at each visit. In order to account for the short term decrement associated with having an acute seizure, the EQ-5D-5L Telephone version will also be collected through a telephone interview with a research nurse when the participant experiences their first episode of seizure like symptoms during the trial period. Separately, data will be collected to determine whether the suspected seizure was a seizure or not. Only utilities of events shown as seizures will be used in the assessment of cost-effectiveness.

The EQ-5D-5L is a standardised and validated generic instrument that is widely used in economic evaluations, and has been validated in many patient populations and using numerous modes of administration. Proxy versions of the EQ-5D-5L and a face to face version will be available to help the patient/carer as described in Section 2.5. The responses to the EQ-5D-5L will be converted into health state valuations using the recently published value set [46].

Although the descriptive system for the EQ-5D-5L has been validated by National Institute for Health and Care Excellence (NICE), to date the valuation set has not. Therefore, as a sensitivity analysis, the responses to the EQ-5D-5L will also be converted into health state valuations by mapping the EQ-5D-5L descriptive data onto the EQ-5D-3L value set using the

mapping function validated by NICE [47]. Both sets of utility values will then be combined with the study participant's mortality to estimate QALYs for each trial participant, using the 'under the curve' approach [48]. A mean QALY per intervention arm will then be estimated.

Data analysis

Once mean costs and QALYs have been calculated, these values will be presented for the two randomised group, as well as incremental mean costs and QALYs calculated with the incremental cost per QALY gained at 12 months. As the trial follow up period is 12 months, costs and effects will not be discounted.

These data will be analysed using both the trial data (unadjusted costs and effects) and regression analyses, specifically seemingly unrelated regression models [49], which can simultaneously estimate both costs and health outcomes at the individual level whilst taking into account the fact that the contemporaneous error terms may be correlated. Statistical imprecision will be presented as confidence intervals around differences in effectiveness, cost and cost-effectiveness.

Procedure for Accounting for Missing, Unused

Missing, Spurious or unused data will be handled using appropriate statistical methodologies, for example multiple imputation and inverse probability weighting. The exact method will be determined by the pattern of missing data. Procedures will be detailed in the Data Management and Statistical Analysis Plan.

Sensitivity analysis

A number of sensitivity analyses will be explored. Firstly, deterministic sensitivity analysis will be performed to explore a number of key uncertainties, for example the values of unit costs. These uncertainties will then be combined with a stochastic analysis using non-parametric bootstrapping methods to explore the statistical imprecision surrounding these estimates of costs and effects, in order to generate the data necessary for the presentation of cost and QALY plots, as well cost-effectiveness graphs and cost-effectiveness acceptability curves (CEACs). A CEAC shows the probability that each intervention is cost-effective conditional on a range of possible threshold values that NHS decision makers attach to an additional QALY (e.g. £20,000 per QALY).

2) Assessment of utility associated with seizures

Although the EQ-5D-5L data, collected at fixed time intervals during the trial, may be a good indication of the patients' level of utility at those times, it could be the case that this tool will not fully capture utility over the full study follow-up period. This is because the patients' utility values are likely to vary substantially between the seizure free days and the days in which they suffer from seizures.
Therefore, to complement the main analysis (which will only use the responses to the EQ-5D-5L questionnaire at the fixed time intervals), two methods will be used as part of sensitivity analyses. Firstly, trial participants will be asked to complete a telephone version of the EQ-5D-5L the first time they experience seizure like symptoms during the trial period. The utility values generated from these responses will then be integrated into the within-trial analysis to take account the short-term impact on utility caused by seizures and suspected seizures that occur in between the data collection points.

The second approach, to complement the main analysis will be to use a standard gamble (SG) exercise to derive utility values for patients when suffering seizures. The SG technique is a well-established way of measuring the utility of specified health states[50], and is generally considered to have the strongest theoretical background of the choice-based valuation methods commonly used to weight different health states [51], as it is based upon the theory of rational decision-making under uncertainty or risk [52]. The 'conventional' or 'chained' versions of the SG will be used depending on the specific nature of the health state[53].

The descriptions of a variety of different health states that will be valued in the SG will be developed in collaboration with clinicians and a Patient and Public Involvement (PPI) group external to the study. The SG will be administered through an online survey developed with a survey company. Two separate samples will complete the survey. The first sample who will complete the survey will be general population sample of the United Kingdom. The target sample for this sample will be 300 respondents. Recent work by NICE has argued that although patient preference studies have a place in HTA decision making in certain areas, they should not be directly into health economic modelling, as this does not align with the current recommended methods[54]. Specifically, the NICE guidelines state that the source of the data for valuing changes in health-related quality of life should be taken from a sample representative of the UK population ([55]). However, a number of recent studies (for instance Versteegh & Brouwer 2016 [56]) have argued from both a theoretical and practical perspective that both patient and general public preferences are a valid source of utility values in economic evaluations, and in principle could be combined when measuring patient benefit. Therefore, we will also ask a group of former patients to complete the survey. These former patients will be recruited through relevant clinical and charity email lists (for example, the email list of the Brainstrust). The target sample size for this sample will be 100 respondents.
In a similar manner to the approach used to incorporate the results of the telephone version of the EQ-5D-5L, the utility values generated from the SG responses will be

then integrated into the within-trial analysis to take account the short-term decrement in utility caused by seizures and suspected seizures that occur in between the data collection points.
In order to use both responses to the telephone version of the EQ-5D-5L and responses of the SG, we will also need to have an estimate of how long the effects of a seizure or suspected seizure lasts. Estimates of the length of effect of a seizure or suspected seizure will be based on clinical and patient guidance (based on advice of the Patient and Public Involvement (PPI) group external to the study). Specifically, during the trial period, clinician experts and the PPI group will be consulted to estimate the length of time that a patient might spend suffering from different types of seizure (e.g. Simple Partial Seizure, Complex Partial Seizure, Partial Seizure with Secondarily Generalized Seizure). A plausible range of values for each main type of seizure will be collected and used in the empirical analysis.

3) Model based economic analysis

As the benefits of the intervention are expected to last beyond the 12 month trial follow-up period, an economic model will be developed in a suitable software package (e.g. R or TreeAge) to estimate the cost-effectiveness of the intervention with other relevant managements of seizures (including the trial control intervention) suffered by those with cerebral glioma over a longer time frame. The economic model will follow guidance for good practice in conceptualising an economic model [57] and, where appropriate, will also be informed by advice from clinical experts in the area of neuro-oncology.

Although the exact form of the economic model has yet to be finalised, it is anticipated that it will take the form of a state transition model, with the time horizon of the model being the expected lifetime of those with glioma. As with the within-trial analysis, this economic model will take the perspective of the NHS, personal social services and costs borne by patients and their families, for example out of pocket expenditure on health care.

Trial data will be a vital source for populating the model, with additional data on health state utilities and the probabilities of future events required to populate the model beyond the 12 month trial period being based on a structured literature review. Utility scores will be calculated based on responses to the EQ-5D-5L questionnaire from participants in both the intervention and control arms of the randomised control trial (RCT). These will also be cross validated with existing values from the literature.

The use of services for the treatment and management of cerebral glioma will also be modelled. The costs of these events will be based upon the estimates for these events derived from within the trial and will also be supplemented by focused searches of the literature and health economic databases (e.g. the Centre for the Evaluation of Value and Risk in Health, the Cost-Effectiveness Analysis Registry and the NHS Economic Evaluation Database) to update the estimates used within our existing models.

The output of the economic model will be used to produce estimates of costs, effects, incremental costs, QALYs, and ultimately measure cost-utility. Cost-effectiveness will be reported as incremental cost per QALY gained over the patient's lifetime. As the duration of the model-based analysis is greater than one year, both costs and effects will be discounted at 3.5% in the base case analysis where appropriate, in line with current guidance from NICE [58].

To explore uncertainty in the model parameters such as variations in unit prices, and parameter statistical imprecision we will conduct extensive deterministic (e.g. for unit prices) and probabilistic (for statistical imprecision) sensitivity analyses. For the latter we will attach appropriate distributions to the model input parameters. This method requires treating each input in the model as a distribution and using Monte Carlo simulation. The results from this analysis will be presented as plots of costs and QALYs derived from the probabilistic analysis and Cost-Effectiveness Analysis Curves.

8. ACCESS TO SOURCE DATA/ DOCUMENTS

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the Sponsor, SCTRU or the Coordinating Centre, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorised individuals.

Before site a site is initiated, a disclaimer will be signed detailing which data points are to be captured on a paper copy within the patient file.

9. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control will be maintained through adherence to good clinical practice (GCP) and the coordinating centre's standard operating procedures (SOP)s. The coordinating centre will monitor that CRFs are being entered remotely in a timely manner and will evaluate entered CRFs for compliance with the protocol, inconsistencies and missing data.

9.1. Monitoring Visits

We have allowed for site visits in the UK to enable monitoring by SCTRU to check patient consent forms, confirm compliance with the protocol and complete source data verification (SDV) on the patient data as defined in the Data Monitoring Plan. Higher levels of monitoring will be performed, if requested, by the Data Monitoring Committee (DMC), or if the investigators, the Trial Management group or Trial Steering Committee identify particular safety issues**.**

Participating centres may be monitored by SCTRU to confirm compliance with the protocol and complete source data verification (SDV).

10. ETHICAL CONSIDERATIONS

Ethical approval by a Multi-Centre Research Ethics Committee will be needed before the trial can be started. The trial will be carried out according to guidelines of good clinical practice (GCP) as defined by paragraph 28 and Schedule 1 Part 2 of the Medicines for Human Use

(Clinical Trials) Regulations, 2004, and the Clinical Trials Directive (2001/20/EC) elsewhere in the EU and follow the principles of research governance.

10.1. Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number (Community Health Index and/or hospital number in Scotland) will be collected to enable tracing through national records. The personal data recorded on all records will be regarded as confidential, and to preserve each patient's anonymity, only their initials and date of birth will be recorded on CRFs. The patients will be identified within the CRFs by the use of a unique trial number allocated to them upon entry into the study.

The Principal Investigator (or delegate) at each site must keep a consent log. The Principal Investigator must ensure that patient confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

SCTRU will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. SCTRU will request the patient Date of Birth only on the Demographics CRF, all other CRFs will only utilise patient initials and assigned trial ID. Any SAE form will derive the patient age from the DOB provided in demographic section.

All patient identifiable data will be handled, computerised and stored in accordance with Data Protection legislation and Public Health Scotland Confidentiality Guidelines.

10.2. Informed Consent

Due to the nature of the trial, patients may present in two categories, those requiring urgent surgery (admitted to hospital, surgery within approximately 7 days) and those who will be outpatients awaiting an elective surgery date.

As such the Informed Consent process must be dealt with according to the patients situation.

Outpatients may be seen prior to their pre-surgical visit, therefore the trial may be discussed with them during these appointments. If the treating clinician will not see the patient at a face-to-face visit prior to the pre-surgical visit, but instead have a telephone/video interview, the patient informed consent may be posted to the patient to allow the patient additional time to consider participation.

Verbal consent can be taken as partial consent over the telephone, prior to the pre-surgical visit. This will allow the site to complete the following steps remotely if required:

- Remote completion of Karnofsky status
- Discussion of patient's medical history
- Documentation of concomitant medications in trial database
- Remote completion of PHQ-9 questionnaire
- Randomisation

The patient identification must be verified at the time of admission for surgery or during the pre-surgical visit. The telephone consent must be paired with the ***Standard Patient Informed Consent*** before completing the following actions:

- Completion of pregnancy test (if applicable)
- Provision of IMP (if randomised to IMP arm)

For patients randomised to the levetiracetam arm the initial levetiracetam supply will be provided at the pre-surgical visit to allow them to start the prophylactic treatment prior to surgery.

Inpatients may be in the position of requiring urgent surgery, the consent and randomisation may have to take place in a short period of time. Prior to randomisation, the trial team must ensure the patient has a minimum of 12 hours prior to surgery to allow for 2 doses of levetiracetam. Care will be taken by the trial team to allow for as much consideration time as possible prior to randomisation. If the patient does not feel able to make a decision with the time available to them they will be excluded from the trial.

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever they want. This will not prejudice the patient's subsequent care.

Documented informed consent must be obtained for all patients included in the study before they are enrolled or randomised. This must be done in accordance with the national and local regulatory requirements and must conform to guidelines on Good Clinical Practice.

All patients must be able to provide informed consent on joining the trial and will have the option to consent to remain in the trial and on IMP (if applicable) should they suffer a decline in cognitive ability at any point during the trial.

All Patient Information Sheets & Informed Consent Forms will be version controlled and dated and this information will always be stated in any communication with ethics committees.

Carers will also be consented to ensure they are able and willing to assist/complete EQ-5D-5L and other questionnaires as required. If a new carer attends a visit and can complete the EQ-5D-5L then they will be consented at that time.

11. RESEARCH GOVERNANCE

11.1. Trial Organisation

Chief Investigator – The Chief Investigator will have overall responsibility for the design, co-ordination and management of the study. These include:

- Trial authorisation including responsibility for the protocol and obtaining approvals
- Ensuring that the trial is conducted according to Good Clinical Practice (GCP)
- Assessment of SAEs and providing a prompt response as to whether the SAE is a SUSAR.

Clinical Trials Unit –The Sponsor has delegated the responsibility for overall project management, data management and monitoring to the Scottish Clinical Trials Research Unit (SCTRU), based in Edinburgh. Responsibilities include:

- Assistance with completion of the IRAS form and MREC communication
- Production of trial specific documentation (i.e. CRFs)
- Assistance with site activation procedures within centres
- Data management
- Financial Management

- Monitoring
- Pharmacovigilance – Reporting of serious adverse reaction (SAR)s / SUSARs

Statistical Analysis – Lisa Hopcroft, based at SCTRU, Edinburgh will undertake the final analysis arising for this study.

Sponsor – PHS will act as study sponsor. Central study co-ordination, data collection, monitoring and organisation of the data for the statistical analyses will be undertaken by SCTRU, which has processes in place to ensure that the study will not open to recruitment until appropriate approvals and authorisations have been obtained from the independent research ethics committee, and NHS Research and Development departments.

Local Project Teams – These will consist of Surgeons and/or Oncologists (responsible for introducing the patient to the study and ensuring eligibility and consent), Research Nurse (responsible for patient recruitment, obtaining consent and co-ordination of all aspects of data collection). Centres are specifically responsible for conducting the trial in accordance with the protocol, Standard Operating Procedures (SOPs), the trial agreement and Good Clinical Practice.

Trial Steering Committee (TSC) – The Trial Steering Committee (TSC), including members of the research team and an independent Chair, will be responsible for the progress and conduct of the study and convene after the scheduled DMC meetings.

Trial Management Group (TMG) – A Trial Management Group (TMG) will meet approximately every 6 months to oversee the operational aspects of the trial. Responsibilities will be outlined within the TMG charter.

The TMG will include consultant neurologists who will work as part of the group to review source documents (or event descriptions) for 10% of all identified seizures. All seizures will be assessed utilising a standard seizure definition (definition of a seizure described in section 2.4).

Any discrepancy in classification between the TMG review and the original investigator decision will be recorded. Numbers of discrepancies will be highlighted to the Data Monitoring Committee.

Data Monitoring and Ethics Committee (DMC) – A Data Monitoring and Ethics Committee will convene 6 monthly initially, and annually thereafter, to review all data including adverse events and develop a stopping policy for the trial, if necessary. Specific issues that will be looked at include: tolerability of initial dose, dose reductions, toxicities (including interaction of the mild increased bleeding risk) & review schedules. There will be an extra meeting of the committee after 50% recruitment.

12. FINANCING AND INSURANCE

This study is funded by National Institute for Health Research (NIHR) and the study IMP is provided by UCB BioPharma. In addition the trial is endorsed by Cancer Research UK's Clinical Trials Awards & Advisory Committee (CTAAC). Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

13. PUBLICATION POLICY

All presentations and publications relating to the trial must be authorised by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by the Trial Management Group, representatives from SCTRU and high accruing clinicians. The trials offices and all participating Centres and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning their patients, which is directly relevant to the questions posed in the trial, until the main results have been published.

14. DISSEMINATION OF RESULTS TO PATIENTS & THE WIDER PUBLIC

The research will be disseminated to the wider public as well as research participants by actively involving patients, participating centres, their staff and via presentation at professional UK/international bodies involved in management of patients with brain tumours (Society of British Neuro-Surgery (SBNS); Association of British Neurologists (ABN); Royal College of Radiologists; British Neuro-Onc Society (BNOS). We will use networks of relevant UK charities through regular research updates and annual publications, including the IBTA magazine (13,000 copies sent to recipients in 113 countries and widely distributed at international neuro-onc and cancer conferences).

The TMG will seek PPI input to develop a dissemination plan so that patients/caregivers understand the findings and can engage confidently with clinicians about the prophylactic use of AEDs. Dr Helen Bulbeck the PPI representative for the trial will convene the PPI panel in order to consult and prepare a formal dissemination plan for the study. Our aim is that there should be a number of options for informing the participants; these could include face to face discussions with their clinician, information placed on the trial website or a trial newsletter sent out to all patients (after seeking ethical approval). We anticipate that the PPI panel will also contribute to the final paper.

Appendix 1 – Principal Investigator Declaration

SPRING
Seizure **PR**ophylaxis **IN G**lioma

Principal Investigator Declaration

I acknowledge receipt of version <#> date <dd/mmm/yyyy> of the SPRING trial protocol (REC approved <dd/mmm/yyyy>) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern.

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please retain original declaration form in the Investigator Site File and return a copy to:
SPRING Team
Scottish Clinical Trials Research Unit
Public Health Scotland
Gyle Square
1 South Gyle Crescent
Edinburgh
EH12 9EB
Email: phs.spring@phs.scot

Appendix 2 – The Principles of ICH Good Clinical Practice

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favorable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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