Surgeons Trial Of Prophylaxis for Epilepsy in seizure naive patients with Meningioma: a randomised controlled trial (STOP'EM)

STOP'EM Protocol
V2.0, 28/03/2023

Study Sponsor(s):
The University of Liverpool, Clinical Directorate
Thompson Yates Building
The Quadrangle, Brownlow Hill,
Liverpool
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Research Ethics Ref: 22/LO/0868

Sponsor Ref: UoL001699

Funder Ref: NIHR129748

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature:  **Date:** 28 Mar 2023

Professor Michael D Jenkinson PhD, FRCS(Neuro.Surg)
Professor of Neurosurgery
Department of Clinical and Molecular Pharmacology
University of Liverpool

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature:  **Date:** 28 Mar 2023

Karen Wilding
Senior Clinical Research Governance Manager
University of Liverpool

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature:  **Date:** 28 Mar 2023

Professor Carrol Gamble
Director of Liverpool Clinical Trials Centre

General Information

This document describes the STOP'EM trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Prof. Michael Jenkinson, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 15.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Health Economics:**
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Liverpool Clinical Trials Centre University of Liverpool 2nd Floor Institute in the Park Alder Hey Children's NHS Foundation Trust Eaton Road Liverpool L12 2AP	Adel Helmy Cambridge Neurosurgical Laboratories Level 6, A-block Addenbrooke's Hospital Hills Road Cambridge CB2 0QQ	Department of Neuroradiology The Walton Centre NHS Foundation Trust Lower Lane Liverpool L9 7LJ

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Health Economics:**
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In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:	**Medical Expert who will Evaluate SAR Reports (1):**	**Medical Expert who will Evaluate SAR Reports (2):**
Mr Adel Helmy Consultant Neurosurgeon Department of Clinical Neurosciences Addenbrooke's Hospital Hills Road Cambridge CB2 0QQ Telephone: 01223 336946 E-mail: aeh33@cam.ac.uk	Professor Tony Marson Professor of Neurology Clinical Sciences Centre Lower Lane Liverpool L9 7LJ Telephone: 0151 529 5705 E-mail: a.g.marson@liverpool.ac.uk	Dr Robin Grant Consultant Neurologist Department of Clinical Neurosciences Royal Infirmary Little France Crescent Edinburgh EH16 4SA Telephone: 07456 973500 E-mail: robin.grant7@gmail.com

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 Table of Contents

2 Glossary

AED	Anti-epileptic drug
AR	Adverse Reaction
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Developmental Safety Update Report
DVLA	Driver and Vehicle Licensing Agency
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
HDPE	High Density Polyethylene
HES	Hospital Episode Statistics
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IEP	Image Exchange Portal
IMP	Investigational Medicinal Product
IPD	Individual Participant Data
ISF	Investigator Site File (part of the Trial Master File)
ITT	Intention-to-Treat
ISRCTN	International Standard Randomised Controlled Trials Number
KPS	Karnofsky Performance Status
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
MHRA	Medicines and Health Care Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PSF	Pharmacy Site File
PSS	Personal Social Services
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

RN	Research Nurse (Registered)
RSI	Reference Safety Information
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
sIMPD	Simplified Investigational Medicinal Product Dossier
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

3 Protocol Overview

Full Title:	Surgeons Trial Of Prophylaxis for Epilepsy in seizure naive patients with Meningioma: a randomised controlled trial
Acronym:	STOP'EM
Phase:	III
Target Population:	Seizure-naïve patients, aged 16 years and above, newly diagnosed with meningioma undergoing surgical resection, attending centres in the UK & IRE
Sample size:	1004 participants
Inclusion Criteria:	1. Newly-diagnosed meningioma on MRI 2. Seizure-naïve at presentation 3. Surgical resection of meningioma planned 4. Age ≥16 years 5. Written informed consent
Exclusion Criteria:	1. Posterior fossa meningioma 2. Previous history of epilepsy 3. Previous history of provoked seizures 4. Previous cranial neurosurgery for any cause 5. Renal failure (Chronic Kidney Disease [CKD] 4-5) 6. Use of anti-epileptic drug for another indication (e.g. trigeminal neuralgia) within 7 days preceding randomisation 7. Known hypersensitivity to levetiracetam, other pyrrolidone derivatives or any of the excipients 8. Actively breastfeeding 9. Weigh below 50kg (if aged 16 or 17 years)
Study Centres and Distribution:	UK & IRE NHS neurosurgical centres
Patient Study Duration:	**Duration of treatment:** 14 days, commencing one day before surgery **Duration of follow-up:** 12 months post-surgery
Study Duration	72 months
	Intervention:

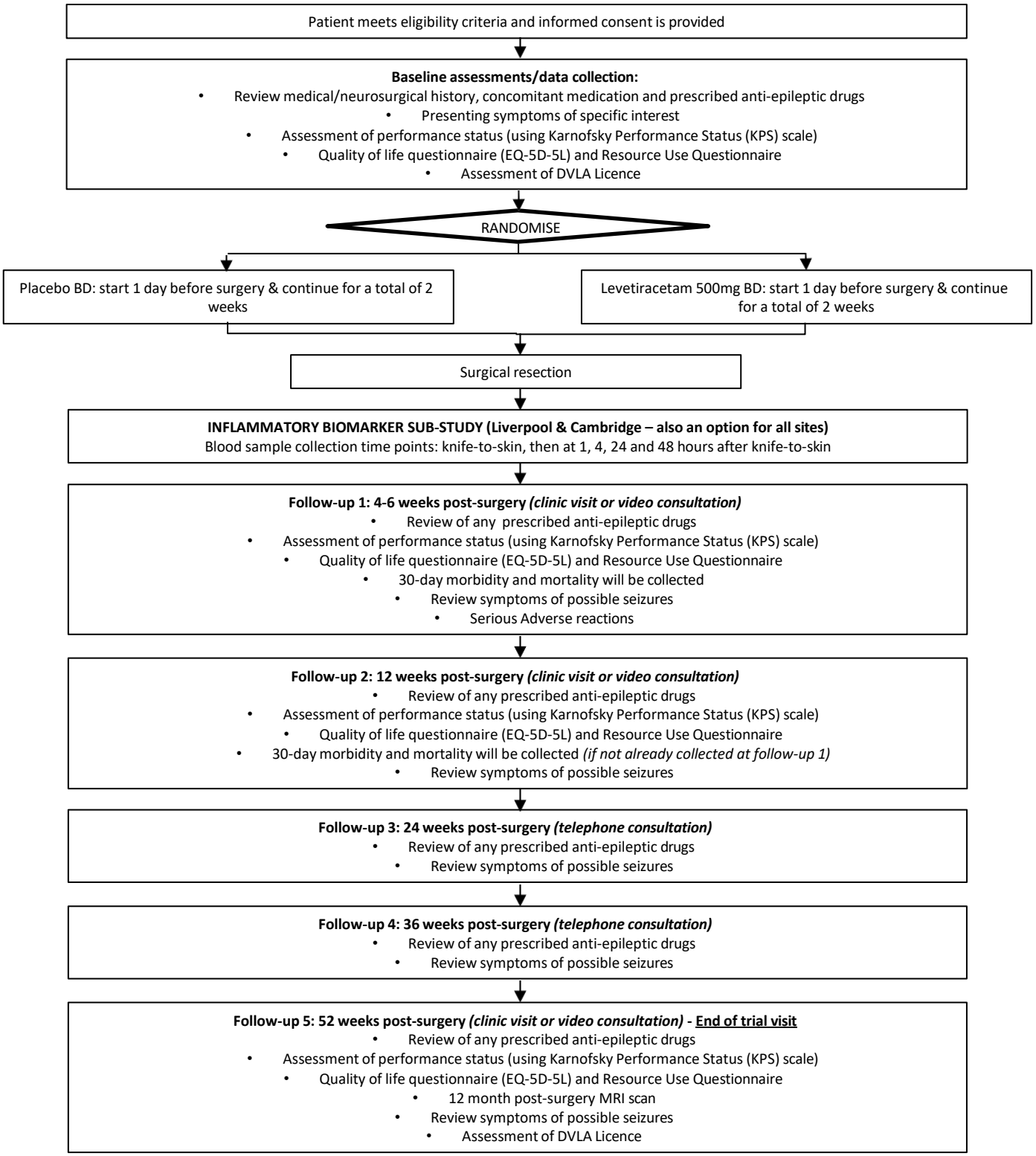
IMP / Intervention:	IMP:	Levetiracetam
	Form:	Over-encapsulated capsule
	Dose:	500mg, twice a day (AM and PM)
	Route:	Oral
	Duration:	14 days, commencing 1 day before surgery
	Comparator:	
	Control:	Placebo
	Form:	Over-encapsulated capsule
	Dose:	Twice a day (AM and PM)
	Route:	Oral
	Duration:	14 days, commencing 1 day before surgery

Objectives:	
Primary objectives	1. To determine whether 2 weeks prophylactic levetiracetam treatment reduces the risk of developing seizures within 12 months of surgical resection of newly-diagnosed seizure naïve meningioma compared to placebo
Secondary objectives:	2. To improve the understanding of the safety of prophylactic levetiracetam 3. To determine whether prophylactic levetiracetam influences quality of life 4. To determine the 30-day morbidity and mortality associated with meningioma surgery
Economic objective:	5. To estimate the cost effectiveness of prophylactic levetiracetam in seizure-naïve meningioma
Exploratory/ Translational objective:	6. To create a repository of MRI scans and blood samples for future research, investigating imaging and blood biomarkers that may predict seizure development

Outcomes:		**Corresponding objective:**
Primary outcome:	1. At least one seizure at 12 months post-surgery	1
Secondary Outcomes:	2. Time to first seizure	1
	3. Time to first convulsive seizure	1

	4. Time to first unprovoked seizure (seizure from day 8 onwards)	1
	5. Driving under licence by12 months	1;3
	6. EQ-5D-5L	3
	7. Serious adverse reactions	2
	8. Landriel Ibañez classification	4
Economic outcomes:	9. Incremental cost per quality-adjusted life year (QALY) gained	5
	10. 12-month resource use associated with NHS and personal social services	5

3.1 Schematic of Study Design



4 Roles and Responsibilities

Sponsor

The University of Liverpool are the Sponsoring organisation and are legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.

Funder

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (HTA), (NIHR129748). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Funder	Financial and Non-financial Support Given	Role
NIHR Health Technology Assessment Programme	Financial support for the delivery of the project	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results for publication or other dissemination.

Chief Investigator: Professor Michael Jenkinson is the Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Co-Chief Investigator: Mr Adel Helmy is the co-chief investigator for the trial and has responsibility for the design and conduct of the trial in collaboration with other members of the study team and under the mentorship of the CI (Michael Jenkinson)

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: LCTC at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, safety reporting, data management, randomisation, statistical analysis, participating site coordination and IMP distribution.

Oversight Committees

STOP'EM trial is subject to oversight from the following committees:

Trial Management Group (TMG)
A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), PPI representation, and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet regularly in accordance with their terms of reference.

Trial Steering Committee (TSC)
The Trial Steering Committee will consist of an independent chairperson, 3 independent experts in the field of neurology, neurosurgery, biostatistics, including PPI representation, the CI and observers. The role of the TSC is to provide oversight of the trial, consider the recommendations of the Independent Data and Safety Monitoring Committee, and provide advice through its independent chairperson.

Independent Data and Safety Monitoring Committee (IDSMC)
The Independent Data and Safety Monitoring Committee (IDSMC) will consist of an independent chairperson, plus 2 independent members; collectively they will have expertise in the fields of neurology and neurosurgery, and biostatistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. They will review data during closed meetings and make recommendations to the TSC concerning the continuation of the study.

Details of the interim analysis and monitoring are provided in Section 13.5 and 14.3 respectively.

4.1 Protocol Contributors

Name	Affiliations	Contribution to protocol
Professor Michael D Jenkinson	University of Liverpool	Study concept, study design, translational research, protocol development
Mr Adel Helmy	University of Cambridge / Cambridge University Hospitals NHS Trust	Study design, translational research, protocol development
Professor Carrol Gamble	University of Liverpool	Statistics, study design, protocol development
Ms Helen Hickey	University of Liverpool	Study design, protocol development
Dr Samantha Mills	The Walton Centre NHS Foundation Trust	Imaging analysis
Dr Robin Grant	Royal Infirmary of Edinburgh, NHS Lothian	Study design, protocol development
Professor Dyfrig Hughes	Bangor University	Health economics, protocol development
Professor Tony Marson	University of Liverpool	Study concept, study design, protocol development
Ms Rebecca Tangney	Aintree University NHS Foundation trust	IMP management and governance arrangements, protocol development
Dr Helen Bulbeck	Director of Brainstrust	Study concept, study design
Mr Usama Ali	Patient group representative – The Chancellor Masters and Scholars of the University of Oxford	Study concept, study design
Mrs Sonia Whyte	University of Liverpool	Protocol development
Miss Priya Francis	University of Liverpool	Protocol development
Mrs Dianne Wheatley	University of Liverpool	Protocol development

5 INTRODUCTION

5.1 Background

Meningioma is the most common primary brain tumour with an incidence rate of 5 per 100,000 person years in the UK. Each year in the UK approximately 1600 participants undergo surgery for meningioma[1]. At the time of diagnosis approximately 70% of patients will not have had a seizure. After surgical resection of the meningioma patients are at risk of developing post-operative seizures. Seizures post-surgery can be divided into two categories:

1. Early (acute symptomatic seizures (i.e., provoked) – in the first week after surgery)[2]
2. Late (unprovoked seizures, i.e., epilepsy – from day 8 after surgery).

Data on the natural history of seizures following surgery for meningioma is of poor quality and mostly from single-centre retrospective studies. A systematic review and meta-analysis showed the development of post-operative epilepsy in up to 21.1% (mean 12.3%) of seizure naive meningioma patients but the timing of seizure onset was not reported[3]. Early post-operative seizures lead to prolonged inpatient stay, delayed neurological recovery, and can be associated with brain swelling and death. Late post-operative seizures within 12 months can have a negative impact on quality of life, return to work, return to driving, and can even result in sudden death[4-7].

The ability to prevent seizures is of great importance to patients and surgeons, however, there is no high-quality evidence on the role of prophylaxis in meningioma surgery. Although several clinical/radiological factors have been reported to be associated with risk of developing post-operative seizures (convexity/parasagittal location, midline shift, peri-tumoral oedema, meningioma volume), these factors are inconsistently reported across studies and are therefore not reliable for use in routine clinical practice to target patients at higher risk of developing post-operative seizures.

A survey of UK neurosurgeons was undertaken with the aim to understand current practice patterns on the use of prophylactic anti-epileptic drugs (AED) in meningioma surgery. Based on responses from 60 neurosurgeons working in 25 adult neurosurgery centres[8] the survey found that:

- 62% do not routinely use seizure prophylaxis.
- 70% have used seizure prophylaxis at some point in the last 5 years.
- AED preference: 55% levetiracetam, 43% phenytoin, 2% valproate.
- Duration of treatment: 63% for either 7 or 14 days.

This survey highlights the variability in practice across the UK with ongoing uncertainties regarding seizure prophylaxis in meningioma surgery, and similar survey data are reported internationally[9]. Seizures and side effects from anti-epileptic drugs (AED) impact a patient's quality of life and can be life-threatening. 70% of the neurosurgeons questioned had administered prophylactic AEDs at some point to prevent seizures despite a lack of evidence to support this. There are currently no clinical studies assessing AEDs in the prophylactic setting for meningioma surgery.

5.2 Rationale

The issue of seizure prophylaxis in meningioma surgery is repeatedly discussed in the neurosurgery literature with calls for well-designed trials to definitively answer the question[10, 11]. The ability to prevent seizures following meningioma resection (i.e., to mitigate one of the adverse effects of surgery) is of great importance to patients and surgeons. Whilst many patients are cured of their meningioma or have long-term tumour control, the development of epilepsy has a major long-term impact on quality of life and health needs[4-7]. Seizures may result in injuries or life-threatening complications such as status epilepticus or aspiration pneumonia. More often, the severity of epilepsy is relatively mild in meningioma patients[5] however seizures still restrict patient's independence. For example, in the UK driving is prohibited for 6-12 months after a

seizure and meningioma surgery, and patients whose jobs involve working in potentially dangerous circumstances (e.g., painters, electricians) become unable to work and suffer financial consequences. Patients may also suffer debilitating anxiety about whether or when a seizure may occur. In patients with meningiomas, seizures can also be associated with worsening of neurological symptoms such as weakness or cognitive function. Seizures in the immediate post-operative period led to prolonged inpatient stay, delayed neurological recovery, and can be associated with brain swelling and death. The prospect of preventing acute symptomatic seizures and epilepsy has major patient and healthcare benefits. Patients who develop seizures are started on an anti-epileptic drug (AED) and levetiracetam is favoured by most neurosurgeons in the modern era. Patients are often prescribed AEDs long term and this is associated with direct healthcare costs of the drug.

Since there are no studies that have addressed the optimal duration of AED treatment in post-meningioma surgery acute symptomatic seizures and epilepsy, and whether and when the drug can be safely stopped, patients can often remain on treatment for life. Consequently, with long-term use the potential side effects and tolerability of levetiracetam are particularly important. Side effects that can have a negative impact on a patient's quality of life include mood disturbance (e.g., anxiety / aggression / irritability), somnolence, fatigue, headache, balance disturbance and vertigo. Indeed, we have shown that the side effects from long term AEDs can have a greater impact on quality of life, than the seizures themselves in patients with epilepsy and meningioma[5]. Therefore, there are clear benefits to patient's well-being and health care services if seizures can be prevented post-surgery in previously seizure-naive patients by a short course of AEDs.

Whilst there is a lack of studies comparing levetiracetam to placebo (or no treatment) in brain tumours (all types), several small, mainly retrospective studies have compared levetiracetam with phenytoin or valproate and the results have been summarised in two separate systematic reviews[12, 13]. These small, underpowered studies of levetiracetam suggest a benefit in seizure prophylaxis compared to phenytoin, and hint at a potential effect on long-term seizure prevention, indeed several animal studies have reported that levetiracetam may have an anti-epileptic mechanism in addition to its anti-convulsant action[14, 15]. Despite this our own systematic review of prophylactic levetiracetam compared to no treatment, for meningioma surgery did not demonstrate such an effect, however, the two groups were highly unbalanced and there were insufficient data to perform a meta-analysis[16]. Nevertheless, when all the existing literature is considered, it supports our choice to use levetiracetam and further highlights the need for a high quality prospective RCT to answer the clinical question: In patients with newly diagnosed meningioma who have never had a seizure and are undergoing surgical resection, does a fourteen day course of prophylactic levetiracetam starting one day before surgery, reduce the risk of developing seizures? STOP'EM will follow patients for a period of twelve months to assess whether a short prophylactic course of treatment with an AED will reduce the risk of developing seizures.

5.3 Risk and Benefits

Potential Risks

This trial is categorised as Type B (Somewhat higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the MHRA.

The potential toxicity associated with a 14-day course of levetiracetam is small, but side effects can occur and these will be recorded as part of the study and the frequency and severity monitored by the IDSMC. Most side effects occur with longer-term use and we therefore do not anticipate a high reporting rate in STOP'EM.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the Trial Master File.

Potential Benefits

For the participant: The potential benefit of seizure prophylaxis in meningioma surgery must be balanced against the risks[4, 5, 13, 17]. There have not been any randomized placebo-controlled trials of prophylactic AEDs in seizure-naive patients with meningioma[18].

The current evidence for seizure prophylaxis in meningioma surgery is limited and there is ongoing uncertainty as to whether it is of benefit[3, 12, 16, 17, 19-23]. However, a recently published (2018) meta-analysis of 352 brain tumour patients from randomized controlled trials, treated using phenytoin as prophylaxis, showed a reduction in acute symptomatic seizure risk within the first week of surgery (RR = 0.352, 95% confidence interval 0.130–0.949, p = 0.039), but no benefit at reducing the proportion with epilepsy at 12 months (RR 1.033, 95% CI 0.498–2.141, p = 0.931)[24]. Whilst this study shows potential benefit, it has limitations: the analysis included only 97 patients with meningioma and adverse events were poorly reported but affected 32% of patients.

Whilst there are a lack of studies comparing levetiracetam to placebo (or no treatment) in brain tumours (all types), several small, mainly retrospective studies have compared levetiracetam with phenytoin or valproate and the results have been summarised in two separate systematic reviews[12, 13]. The first systematic review and meta-analysis of 12 studies (of which only one was randomised and blinded) compared levetiracetam to phenytoin or valproate for prophylaxis in brain tumour surgery and showed a lower adverse event rate and lower overall seizure rate in the levetiracetam group (OR = 0.12 [95% CI 0.03-0.42])[13]. However, there were insufficient data to extract information regarding the incidence of early and late seizures. The second systematic review and meta-analysis of 803 seizure naive brain tumour patients from 7 studies reported a new onset seizure rate of 1.26% in those on levetiracetam, compared to 6.6% in those on phenytoin (OR 0.282, 95%CI [0.117-0.687, p=0.005). In all studies the dose regime and schedule differed and the early and late seizure rates were not reported. Nevertheless, the study shows the potential seizure prevention effect of levetiracetam and indeed the authors call for a trial to compare levetiracetam to placebo[12].

These small, underpowered studies of levetiracetam suggest a benefit in seizure prophylaxis compared to phenytoin, and hint at a potential effect on long-term seizure prevention, indeed several animal studies have reported that levetiracetam may have an anti-epileptic mechanism in addition to its anti-convulsant action[14, 15]. Despite this our own systematic review of prophylactic levetiracetam compared to no treatment, for meningioma surgery did not demonstrate such an effect, however, the two groups were highly unbalanced and there were insufficient data to perform a meta-analysis[16]. Although the existing literature supports the use of levetiracetam it further highlights the need for a high quality prospective RCT to answer the clinical question.

Cost effective: Levetiracetam is cheap (estimated 60 x 250mg tablets: £2.52). There is potential to reduce costs to the NHS and personal social services (PSS) over the 12 months trial follow-up, should it be effective in reducing the risk of seizures. There are no existing studies of cost effectiveness in meningioma with respect to epilepsy therefore an economic evaluation is warranted, to estimate the probability of levetiracetam being cost-effective for broader adoption into clinical practice.

5.4 Objectives

Primary objectives	1. To determine whether 2 weeks prophylactic levetiracetam treatment reduces the risk of developing seizures within 12 months of surgical resection of newly-diagnosed seizure naïve meningioma compared to placebo
Secondary objectives:	2. To improve the understanding of the safety of prophylactic levetiracetam 3. To determine whether prophylactic levetiracetam influences quality of life 4. To determine the 30-day morbidity and mortality associated with meningioma surgery
Economic objective:	5. To estimate the cost effectiveness of prophylactic levetiracetam in seizure-naïve meningioma
Exploratory/ Translational objective:	6. To create a repository of MRI scans and blood samples for future research, investigating imaging and blood biomarkers that may predict seizure development

6 STUDY DESIGN

STOP'EM is designed as a randomised, placebo-controlled, double-blinded multicentre superiority trial with 1:1 allocation ratio.

As the trial aims to determine if prophylactic levetiracetam may reduce sezuires following surgical resection of meningioma when compared to standard care (no additional drug treatment), there is no suitable active comparator and a placebo will be used to provide control data. Attrition bias will be minimised by analysing data based on the principle of intention-to-treat (ITT).

6.1 Blinding

6.2 Who is blinded

Participants and site personnel will be blind to treatment allocations, though individual allocation information can be disclosed where required, e.g. for immediate clinical need. For unblinding procedures see section 8.10.

Within LCTC knowledge of treatment allocation will be restricted to those who have an explicit need to know this information in order to undertake their delegated function.

Members of the Trial Steering Committee will not see data summaries split by treatment group. Members of the Independent Data and Safety Monitoring Committee will see data summaries split by treatment group and individual treatment allocations for assessment of safety events.

At each participating site, pharmacy will be unblinded to treatment allocations.

How the blind will be maintained

Randomisation confirmations, other than those issued to pharmacy, will not include information that will unblind the recipients. Levetiracetam and matching placebo will be over-encapsulated to maintain blinding of participants and site teams.

6.3 Study Setting

Participants will be identified and recruited from specialist neurosurgery units in the UK & IRE. Follow up will occur at home or at the hospital, dependent on visit requirements and local NHS Trust policy.

Selection of Participating Sites

Participating sites must have a suitable Principal Investigator whocan undertake essential roles, and must have sufficient support of other key staff.

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the STOP'EM trial and will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC.

Selection of Principal Investigators

Principal Investigators will be required to have equipoise and to demonstrate relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical

expertise necessary to conduct the study in accordance to the protocol and all regulatory requirements. The trial will be registered for the NIHR Associate PI Scheme.

Suitable co-investigators will be identified at each site to deputise in case of PI absence.

6.4 Internal Pilot

During the 24 month internal pilot phase we will:

Stage 1 – 12 months from recruitment start

Establish feasibility of site opening & recruitment. We will employ the following traffic-light stop/go criteria with regards proceeding to the full trial:

	Red	Amber	Green
Consent	<50%	50-69%	≥70%
Recruitment rate / site / month	<0.6	0.6-1.19	≥1.2
Number of patients recruited at 12 months	<85	85-169	170
Total recruitment	<50%	50-99%	>100%
Number of sites opened	<10	10-19	≥20
Withdrawal/attrition	≥10%	5-9%	≤5%

Where feasibility indicators are in red or amber categories then mitigating reasons and modified strategies will be considered.

Stage 2 - 24 months from recruitment start

Since the primary outcome is proportion with seizures at 12 months post-surgery, and in order to ensure there are sufficient patients with events (seizure), this will be assessed 24 months into the trial to allow for 12 months follow-up. If the control group event rate sample size assumptions are met the trial will continue. In the event of changes to the sample size being recommended then a proposal will be developed for the funder to consider.

7 ELIGIBILITY CRITERIA

All participants must provide written, informed consent before any study procedures occur (see Section 10 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

7.1 Inclusion Criteria

1. Newly-diagnosed meningioma on MRI
2. Seizure-naïve at presentation
3. Surgical resection of meningioma planned
4. Age ≥16 years
5. Written and informed consent

7.2 Exclusion Criteria

1. Posterior fossa meningioma
2. Previous history of epilepsy
3. Previous history of provoked seizures
4. Previous cranial neurosurgery for any cause
5. Renal failure (Chronic Kidney Disease [CKD] 4-5)
6. Use of anti-epileptic drug for another indication (e.g. trigeminal neuralgia) within 7 days preceding randomisation
7. Known hypersensitivity to levetiracetam, other pyrrolidone derivatives or any of the excipients
8. Actively breastfeeding
9. Weigh below 50kg (if aged 16 or 17 years)

7.3 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials during their participation in STOP'EM. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the STOP'EM trial (e.g trials involving only questionnaires, genetic studies, gifting of tissue samples), this must first be discussed with the LCTC who will contact the Chief Investigator (Professor Michael Jenkinson) or co-CI (Mr Adel Helmy).

Individuals who have participated in a trial of any anti-epileptic drug within 7 days preceding randomisation will be ineligible for the STOP'EM trial.

8 TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

Eligible patients will be randomised to receive levetiracetam 500mg or placebo twice a day. Both the IMP and placebo are administered twice daily, AM and PM. The trial is blinded so active and placebo bottles will be labelled with Annex 13-compliant labels and the same method of administration will be applied to both arms (oral administration).

IMP will be procured and packaged by Royal Free Pharmacy Production Unit in accordance with all applicable guidelines.

8.2 Trial Treatment

Treatment Arm - Levetiracetam

Brand name / Active ingredient:	Levetiracetam
Formulation:	Over-encapsulated capsule for oral administration
Dose:	500mg twice a day for 14 days
Manufacturer:	Royal Free Pharmacy Production Unit
Packaging, storage:	Gelatin-coated and over-encapsulated capsules are supplied in high density polypropyline (HDPE) bottles with a polypropylene cap. The product does not require any special storage conditions.
Supplier's name:	Royal Free Pharmacy Production Unit
Regulatory Status:	Market Authorised

Control Arm - Placebo

Brand name / Active ingredient:	Placebo
Formulation:	Over-encapsulated capsule for oral administration
Dose:	N/A
Manufacturer:	Royal Free Pharmacy Production Unit
Packaging, storage:	Gelatin-coated and over-encapsulated capsules are supplied in HDPE bottles with a polypropylene cap. The product does not require any special storage conditions.
Supplier's name:	Royal Free Pharmacy Production Unit
Regulatory Status:	Unlicensed

8.3 Manufacturing and Distribution

Packaging

Both the IMP and placebo treatments will be packaged in high density polyethylene (HDPE) bottles and participants will be dispensed sufficient IMP/placebo for 14 days of treatment, divided into two bottles (see section 8.4.1). The two bottles will be packaged within a fitted carton.

Bottles will be sealed with child-resistant and tamper-evident caps, by Royal Free Pharmacy Production Unit, in accordance with the applicable regulations.

Labelling

The IMP and placebo bottles will be labelled by the distributor(s) with Annex 13-compliant labels. Unblinded secondary tear-off labels will be used – the tear-off portion will be removed by local pharmacy in order to provide participants with blinded treatment. Each bottle will be labelled and used for STOP'EM trial use only.

Shipment

The shipments transported via a GDP-approved courier service. No special conditions are required for shipping.

Regulatory Release to Site

This will be performed by the QP from Royal Free Pharmacy Production Unit. A separate document will be generated to detail how the drug will be distributed.

Storage and Stability

The IMP requires no additional monitoring beyond that required for the general stock held in pharmacy for routine care.

8.4 Preparation, Dosage and Administration

Prescribing and Dispensing

The allocated treatment will be dispensed by the local trial pharmacist after receiving a study-specific prescription.

Each participant will receive the treatment divided between two bottles as follows:

- 1 bottle containing two days worth of treatment for the day pre-op and the day of surgery
- 1 bottle containing 12 days worth of medication for ongoing treatment post-operatively

Both bottles will be packaged into a fitted carton. Participants will be instructed to use the 'two-day' bottle first and to bring all of their medication with them when attending for surgery. In the event that doses are taken pre-operatively from the 'two-day' bottle as planned and, if surgery is cancelled, a replacement prescription will be issued for administration at the rescheduled surgery. In the event that a participant attends for surgery but does not bring their medication with them, a replacement prescription will be issued.

Administration of IMP and Comparator

The first two doses will be administered in the 24 hours prior to planned surgery. The participant will take the medication for 14 days in total.

Levetiracetam – taken orally, 500mg (taken as 2 x 250mg over-encapsulated capsules), twice a day (AM and PM), taken at approximately the same times each day, spaced as close to 12 hours apart as possible.

Placebo – taken orally, 2 over-encapsulated capsules, twice a day (AM and PM), taken at approximately the same times each day, spaced as close to 12 hours apart as possible.

Example dose regime for a patient with surgery scheduled for a Tuesday:

Day 1: Monday: IMP or placebo taken approximately 12 hours apart e.g. 0800 hours and 2000 hours
Day 2: Tuesday (day of surgery): dose taken on morning of surgery, prior to anaesthesia. Dose taken in evening after surgery.
Days 3-14: Wednesday onwards: twice daily dosing as per Monday.

In the event of missed doses this should be recorded on the CRF and the participant should continue and complete the full treatment course. Examples for having a missed dose include:

1. Administration error
2. Participant remains intubated and ventilated after surgery and is therefore unable to take oral medication.

8.5 Treatment Modifications

Participants will be prescribed 500mg levetiracetam (taken as 2 x 250mg) or placebo twice a day for 14 days and no dose modifications are anticipated to be required. Patients in the trial should not be prescribed any other prophylactic anti-epileptic drugs.

The post-operative seizure rate within the first 2 weeks of surgery is approximately 2-3%. In the event that this occurs, the clinical team may stop randomised treatment and unblind the allocation for clinical reasons and this should be recorded in the CRF. Possible clinical scenarios include:

a. Participant randomised to IMP: clinical decision to increase the dose of levetiracetam (this will be off trial using usual NHS procurement and supply arrangements) or to start an alternative anti-epileptic drug
b. Participant randomised to placebo: clinical decision to start an anti-epileptic drug

8.6 Accountability Procedures

Drug accountability logs will be maintained by each site's pharmacy team throughout the trial; pharmacy will maintain an overall inventory of stock received, dispensed, returned, destroyed and quarantined.

If IMP stock received from the distributor is unexpected, wrong, damaged or not within expiry dates, the stock should be quarantined and LCTC contacted for further actions.

If any stock expires at the trial site during the trial or any surplus stock remains at the trial site at trial closedown, this must be notified to the LCTC who will authorise destruction. Stock will be destroyed locally according to site policy and documented in the drug accountability records.

8.7 Assessment of Compliance

Participants will be provided with information regarding the dosing regime. During their first post-operative appointment (4-6 weeks post-surgery), the participant will be asked to confirm if they took all of capsules provided and the response will be be recorded on the relevant eCRF.

8.8 Concomitant Medications/Treatments and Specific Restrictions

Medications Permitted

All medications other than those detailed in the current SmPC and below as prohibited medications are permitted.

Medications Not Permitted/ Precautions Required

Levetiracetam efficacy has been affected when administered with the laxative macrogol. Macrogol should not be taken one hour before and for one hour after taking the study treatment.

Refer to the SmPC ('Special warning and precautions for use') for full information.

Data on Concomitant Medication

Data on the use of levetiracetam and other anti-epileptic drugs will be recorded.

8.9 Overdose

The trial team should ensure participants are advised to always keep the IMP secure. However, if medication is taken in error and exceeds the required dosing regimen, symptoms of overdose observed with levetiracetam are somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma.

In the event of suspected overdose the participant should be unblinded and if it is revealed that the treatment taken is levetiracetam, the stomach may need to be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

Specific information on reporting adverse events can be found in safety section (section 12) and overdoses should be reported as per the procedure specified.

8.10 Unblinding

In the event of an emergency, or if the participant experiences post-operative seizures within the first 2 weeks, a participant may be unblinded by the clinician at the recruiting site by contacting their local pharmacy department. Clinicians carrying out emergency unblinding must be satisfied that knowledge of the treatment allocation is needed to guide the appropriate clinical management of the participant (e.g. management of potential overdose, consideration for treatment of seizure during the two week treatment period). The reason for unblinding must be recorded on the unblinding CRF which should be provided (with all other CRFs completed up to the time of unblinding) to LCTC as soon as possible.

Any participants that are unblinded should remain in the trial and follow-up continued as per protocol.

Accidental Unblinding

If accidental unblinding occurs, this must be reported to the LCTC by use of the unblinding CRF. When reporting include details about:

1. Date of unblinding;
2. Detailed explanation of circumstances;
3. Recipients of the unblinding information;
4. Action to prevent further occurrence (if applicable)

Unblinding at Trial Closure

If participants wish be informed of the treatment allocation they received, they can be provided with this at the end of trial (defined as database lock - see section 10.9) – this information should not be shared before this time point (e.g. upon completion of trial treatment). Any participant unblinding requests will be managed by the site team directly.

9 OUTCOMES

Outcomes:		**Corresponding objective:**
Primary outcome:	1. At least one seizure at 12 months post-surgery	1
Secondary Outcomes:	2. Time to first seizure	1
	3. Time to first convulsive seizure	1
	4. Time to first unprovoked seizure (seizure from day 8 onwards)	1
	5. Driving under licence by 12 months	1;3
	6. EQ-5D-5L	3
	7. Serious adverse reactions	2
	8. Landriel Ibañez classification	4
Economic outcomes:	9. Incremental cost per quality-adjusted life year (QALY) gained	5
	10. 12-month resource use associated with NHS and personal social services	5

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

Individuals attending the participating sites and diagnosed with a meningioma requiring surgical resection will be verbally advised at an appropriate time point that the trial is being conducted and will be asked if they would like further information. If interest is expressed, this will be recorded in the medical notes and trial information will be provided by a member of staff delegated to undertake consent for the trial.

A screening log will be maintained of all the patients referred with a cranial meningioma who do not have seizures, regardless of whether they decide to participate in or are deemed eligible for the trial, to provide important information for monitoring purposes. Reasons for not being eligible and reasons for declining to participate will be asked routinely but it will be made clear that patients or their legal representatives do not have to provide a reason unless happy to do so.

Only a clinician authorised on the site Delegation Log can confirm full eligibility of any patient; a record of this confirmation must be made in the patient's medical notes on the date of screening.

Screening logs will be shared with LCTC for monitoring purposes and to inform on-going study conduct.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason, but will be asked to share the reason if they are willing.

Prospective Informed Consent Process

Written informed consent will be sought from patients who will be approached by a member of the local research team and invited to consider participation.

Patients may be approached at any time point from the first clinical encounter with the neurosurgery team onwards. A written information sheet that forms part of the ethically approved Information Sheet and Consent form will be provided. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ask if they are happy to consent to participation in the trial. Where this is the case, two methods are provided for confirming consent:

1. **Electronic-consent:** If Electronic-consent is required, the patient's email address must be provided to the site. The member of the local research team speaking with the patient must ensure they are fully informed that their email address will be used for this purpose. Full guidance on obtaining consent electronically can be found in STOP'EM Electronic-consent guidance document.
    a. Note, where a witness is used (e.g. if a patient is visually impaired), or where a translator is used (where English is not the patient's first language), electronic-consent **cannot** be used – paper-consent must be used.

    The eConsent must be countersigned and dated by the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

    Once complete, all signatories and LCTC will receive a copy of the final signed consent form.

    Electronic consent may be provided at any mutually convenient time point, but must allow time for the patient to take IMP/placebo 1 day before surgery.

2. **Paper-consent:** If the patient would prefer to use Paper-consent, written informed consent will be obtained by means of a wet-ink dated patients signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.
    a. Note, where a witness is used (e.g. if a patient is visually impaired), or where a translator is used (where English is not the patient's first language), the witness/translator must personally sign and date the consent form in the appropriate field. They must be present during the **whole consent process** and their details should be provided in the medical notes.

    Written consent may be provided at any mutually convenient time point, but must allow time for the patient to take IMP/placebo 1 day before surgery.

    The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:
    - One copy provided to the patients for their information,
    - One copy transferred to the LCTC via encrypted email/secure file transfer service
    - One copy filed in the participant's medical records paper/electronic.

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

Paper consent forms must be transferred separately to any other study documentation.

10.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's Eligibility eCRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation).

Ineligibilty, and reasons for this, must be recorded on the screening log and in patient notes. Patients deemed ineligible must not be randomised to the trial.

Special note for participants with QT interval prolongation: Participants will have ECG as part of the routine pre-operative work-up. Participants with prolonged QT interval (QT interval >500 milliseconds) will be managed as per local routine clinical pathways.

10.4 Baseline Assessments

After confirming eligibility and obtaining written informed consent, baseline assessments should be completed as per the Schedule of Assessments (Section 10.7) in order to accurately complete the Baseline CRF and collect the necessary information for the trial analyses. This includes the following assessments/data:

- Medical / neurosurgical history will be reviewed and recorded on the appropriate eCRF.
- Presenting symptoms of specific interest will be collected.
- Performance status (using Karnofsky Performance Status [KPS] scale) will be assessed (see section 21.2).
- Quality of life using EQ-5D-5L questionnaire will be completed by the participant and collected.
- Resource use using Resource Use Questionnaire will be completed by the participant and collected.
- Participants will be asked about their DVLA Licence status.

Routinely collected information can be transcribed from the patient's medical notes into the eCRF once appropriate consent has been obtained. The patient's GP will be sent a letter to advise of their patient's involvement in the trial.

10.5 Randomisation Process

Elibigility and baseline assessments will occur prior to surgery, either at the pre-admission visit or on the ward as an in-patient, typically within 2 weeks of surgery.

Once the baseline assessments are complete the participant can be randomised. Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive either levetiracetam or placebo in a ratio of 1:1. Randomisation can occur at any time once:

a) Eligibility is confirmed
b) Fully informed written consent has been appropriately documented
c) Baseline assessments have been completed.

After completing the relevant training, designated research staff within site will be issued with a personal login username and password to access the randomisation system.

When patient consent and full eligibility are confirmed in the system, a unique trial number (randomisation number) will be displayed on a secure webpage and an automated email confirmation will be sent to the delegated pharmacy to confirm treatment allocation. Other designated personnel (e.g. randomising researcher, site PI, LCTC trial manager) will receive a separate email confirming that randomisation has taken place without revealing treatment allocation.

Randomisation: web access https://rand.lctc.org.uk/STOPEM

If there are any problems with the randomisation systems contact LCTC on 0151 795 1732 or via email on stopem@liverpool.ac.uk

(Note that the LCTC is open 0900 – 1700, Monday – Friday, excluding public holidays)

Randomisation System Failure

In the event of a randomisation system failure, the site should contact the LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to resolve the problem.

10.6 Intervention

Following randomisation, participants should receive their randomised treatment allocation, as described in Section 8.4, within an appropriate timeframe to allow them to commence the medication on the day before surgery.

10.7 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Schedule of Assessments:

						Follow-Up Schedule				
Procedures	Screening	Baseline[a]	1 day before surgery, continuing for a total of 2 weeks	Day of surgery	Knife-to-skin, then at 1, 4, 24 and 48 hours after knife-to-skin	***Follow-up 1:*** 4-6 weeks post-surgery[c]	***Follow-up 2:*** 12 weeks (±4 weeks) post-surgery[c]	***Follow-up 3:*** 24 weeks (±4 weeks) post-surgery[d]	***Follow-up 4:*** 36 weeks (±4 weeks) post-surgery[d]	***Follow-up 5:*** 52 weeks (+8 weeks) post-surgery[c]
Signed Consent Form and Patient Identifiable Data	X	X								
Assessment of Eligibility Criteria	X	X								
Medical/Neurological History	X	X								
Concomitant Medications/Anti-epileptic drugs	X	X				X	X	X	X	X
Assessment of Performance Status (using KPS scale)		X				X	X			X
Quality of Life Questionnaire – EQ-5D-5L		X				X	X			X
Resource Use Questionnaire		X				X	X			X
MRI scan	X[b]									X
Randomisation		X								
Trial intervention (IMP or Placebo) adherence			X	X		X	*(X)*			
Blood sample (Inflammatory Biomarker Sub-study)					*(X)*					
30-day morbidity and mortality assessment						X	*(X)*[e]			
Symptoms of possible seizures						X	X	X	X	X
Recording of Serious Adverse Reactions			X		X	X	*(X)*	*(X)*	*(X)*	*(X)*
Assessment of DVLA Licence		X								X

[a]At baseline, all procedures should be done before trial intervention
[b]Baseline pre-operative MRI scan
[c]Clinic visit (face-to-face or video consultation)
[d]Telephone consultation
[e]If not done completed at follow-up 1

Follow-up 1: 4-6 weeks post-surgery (clinic visit – face-to-face or video consultation)

This will be conducted where possible during a scheduled hospital appointment where the participants progress will be evaluated and the following information collected:

- Details of any Anti-Epileptic Drug (AED) prescribed.
- Symptoms of possible seizures reviewed.
- Performance status assessed using Karnofsky Performance Status [KPS] scale.
- Quality of life using EQ-5D-5L questionnaire (participant completed or interviewer).
- Resource Use Questionnaire will be completed and collected (participant completed or research team, if remote).
- 30-day morbidity and mortality will be collected using Landriel Ibañez classification system (see section 12.3).
- Any Serious Adverse Reactions will be recorded.
- The participant will be asked to confirm treatment compliance, willingness to continue and be advised about the next visit.

Checks on suicidal ideation and psychosis should be made and managed clinically as per routine practice.

In patients who develop seizures after completing the 14-day course of trial treatment, any investigations/ treatment will be coordinated as per usual NHS practice. Participants will not be unblinded as the study treatment has stopped and the participant will remain on study and continue follow-up for 12 months. Information about the commencement of AED will be collected.

Follow-up 2: 12 weeks (±4 weeks) post-surgery (clinic visit – face-to-face or video consultation)

This will be conducted where possible during a scheduled hospital appointment where the participants progress will be evaluated and the following information collected:

- Details of any AEDs prescribed.
- Symptoms of possible seizures reviewed.
- Performance status assessed using Karnofsky Performance Status [KPS] scale.
- Quality of life using EQ-5D-5L questionnaire (participant completed or interviewer).
- Resource Use Questionnaire will be completed and collected (participant completed or research team, if remote).
- 30-day morbidity and mortality will be collected using Landriel Ibañez classification system (*if not already collected at Follow-up visit 1*).
- The participant will be asked to confirm treatment compliance (if not confirmed at follow-up 1) confirm willingness to continue and advised about the next visit.

Checks on suicidal ideation and psychosis should be made and managed clinically as per routine practice.

Follow-up 3: 24 weeks (±4 weeks) post-surgery (telephone consultation)

This is a scheduled telephone visit and will be a discussion between the participant and a staff member.

- Details of any Anti-Epileptic Drug (AED) prescribed.
- Staff will collect details of any potential seizure symptoms.
- The participant will be asked to confirm willingness to continue and be advised about the next visit.

Follow-up 4: 36 weeks (±4 weeks) post-surgery (telephone consultation)

This is a scheduled telephone visit and will be a discussion between the participant and a staff member.

- Details of any Anti-Epileptic Drug (AED) prescribed.
- Staff will collect details of any potential seizure symptoms.
- The participant will be asked to confirm willingness to continue and be advised about the next visit.

Follow-up 5: 52 weeks (+8 weeks) post-surgery (clinic visit – face-to-face or video consultation)

The participant will be asked to attend the hospital, where possible this will be combined with a scheduled visit and the following information collected:

- Details of any Anti-Epileptic Drug (AED) prescribed.
- Symptoms of possible seizures reviewed.
- Performance status assessed using Karnofsky Performance Status [KPS] scale.
- Quality of life using EQ-5D-5L questionnaire (participant completed or interviewer).
- Resource Use Questionnaire will be completed and collected (participant completed or research team, if remote).
- Routine 12-month post-surgery MRI.
- Participants will be asked about DVLA licence status.
- The participant will be advised study completion is now complete and no further study visits will be required. The results of the study will be reported in the future and shared with participants via social media and the study website.

Landriel Ibañez Classification system

The Landriel Ibañez classification system will be used to collect data on the 30-day morbidity and mortality from meningioma surgery[25]. The system provides a practical and reproducible way to record morbidiy and mortality based on the treatment used to treat the complication. Surgical complications will be recorded – these are define as 'events directly related to surgery or surgical technique'. The table below provides examples of surgical complictions that may arise from meningioma surgery.

Table 1: Classification of Neurosurgical Complications and examples related to meningioma surgery (adapted[25])

Grade I	**Any non-life-threatening deviation from normal postoperative course not requiring invasive treatment**
Grade Ia	*Complication requiring <u>no drug</u> treatment* • Transient new neurological deficit (e.g. hemiparesis, dysphasia, cranial nerves etc.) • Subcutaneous CSF accumulation • Transient diabetes insipidus requiring no drugs
Grade Ib	*Complication requiring <u>drug</u> treatment* • Seizures requiring anti-epileptic drugs • CSF infections requiring antibiotics • Sinus thrombosis requiring anticoagulation • Diabetes insipidus requiring drug treatment
Grade II	**Complication requiring invasive treatment such as surgical, endoscopic or endovascular interventions**
Grade IIa	*Complication requiring intervention <u>without</u> general anaesthesia* • Dehiscent non-infected wound requiring closure under local anaesthesia • Subgaleal CSF collection (pseudomeningocoele) requiring lumbar drain

Grade IIb	*Complication requiring intervention <u>with</u> general anaesthesia* • CSF leak requiring surgical repair • Wound infection requiring surgical lavage / bone flap removal • Pseudomeningocoele requiring external ventricular drain or shunt
Grade III	**Life-threatening complication that may require management in critical care**
Grade IIIa	*Complication involving <u>single</u> organ failure* • Acute hydrocephalus requiring external ventricular drain or shunt • Intracranial haematoma requiring re-operation • Cerebral oedema requiring intubation
Grade IIIb	*Complication involving <u>multiple</u> organ failure* • Meningitis and pneumonia (or other organ failure e.g. renal) • Intracranial hypertension and haemodynamic instability • Ischaemic stroke and pneumonia (or other organ failure e.g. renal)
Grade IV	**Complication resulting in death**

Process for Monitoring Seizures

Patients will be given contact details for the site research team, as well as a checklist of symptoms to look out for that might be seizures. If a patient develops any of these symptoms, they will contact the research team. The patient will be assessed by the research team to see if the symptoms are consistent with seizures.

As per routine clinical pathways, local neurology input may be required to confirm the diagnosis and commence appropriate anticonvulsant medication.

MRI scans

MRI will be performed in all participants as per routine clinical practice at baseline (pre-operatively) and 12 months. Details of imaging sequences are given in the separate MRI manual, alongside instructions on how to transfer pseudoanonymised images to The Walton Centre.

Efficacy Assessments

Details of signs and symptoms of possible sezuires, and of any AED prescribed will be collected at every follow-up time point.

Safety Assessments

All participants will complete a symptoms checklist, administered by a research nurse, 4-6 weeks post-surgery (follow-up 1). This will help determine any adverse reactions specifically related to the IMP.

Quality of Life Assessments

The EuroQOL EQ-5D-5L questionnaire will be administered at baseline, 4-6 weeks (follow-up 1), 12 weeks (follow-up 2) and 52 weeks post-surgery (follow-up 5).

Health Economic Assessments

Hospital resource use will be estimated from patient-level Hospital Episode Statistics (HES) obtained from NHS Digital.

10.8 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

Premature Discontinuation of Study Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Participant-led i.e. request by the participant / legal representative
- Unacceptable toxicity (see Section 11 for Adverse Event reporting)
- Intercurrent illness preventing further treatment.
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Reasons of non-adherance or non-compliance with treatment or other trial procedures
    - Participant develops renal failure that is a contraindication to levetiracetam

Discontinuation from study intervention does not mean discontinuation of the study altogether, and the remaining study procedures, follow up assessment / visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn) prior to unblinding.

Participant Withdrawal from Follow Up

Participants are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study and the LCTC should be informed via email to the LCTC and via completion of a Withdrawal CRF to be returned to the LCTC within 7 days.

If participants express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, or if for example data from routine assessments can still be collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SARs will be notifiable to the LCTC via processes detailed in Section 12 even if a participant has withdrawn from follow up.

Participant Transfer

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via GP.

For all transfers, a transfer case report form (CRF) will be completed by the current site and returned to LCTC. LCTC will then forward the transfer CRF on to the new site; the PI at the new site will be asked to sign this CRF and return to LCTC to confirm that they are taking over responsibility for the participant in the trial.

The current centre should provide a copy of the participant's full CRF to the new site. The participants remains the responsibility of the original site until the new site PI has signed the transfer CRF.

If participant transfer to another participating centre is not possible then the participant would be considered as lost to follow-up.

Loss to Follow-up

A participant will be considered lost to follow up if s/he fails to return for scheduled visits and is not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following action must be taken:

- Sites should attempt to contact the participant and reschedule the missed visit within the given windows and advise the participant on the importance of maintaining the assigned visit schedule.

10.9 End of Trial

The end of the trial is defined to be the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database.

Individual sites may be closed to recruitment prior to their intended recruitment end date if the TMG have concerns about their capacity or capability to deliver the trial, or for operational reasons whereby resources are better used at sites with better capacity to recruit.

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and competent authority e.g. MHRA.
- Trial-related materials reconciled and returned/disposed of as appropriate
- All site data entered onto the study database, discrepancies raised and satisfactory responses received
- Quality Control checks of the Investigator Site Files, Pharmacy Site Files and Trial Master File as appropriate.

11 SUB-STUDIES/NESTED STUDIES

STOP'EM will yield a valuable repository of blood samples and MRI scans. The planned analyses/sub-studies will not be part of STOP'EM itself and is not funded by NIHR as part of NIHR129748, but will form part a separate 'study within a trial' application for a PhD research fellowship.

Sub-study 1 (inflammatory biomarkers) **[optional for sites]**
Two participating study sites (Liverpool and Cambridge) will consent participants to donate blood samples which will be used for future studies to identify inflammatory biomarkers. Blood samples will be taken at 5 time-points:

- knife-to-skin
- 1 hour after knife-to-skin
- 4 hours after knife-to-skin
- 24 hours after knife-to-skin
- 48 hours after knife-to-skin

Samples will be centrifuged; red cells and supernatant will be stored in aliquots at -70°C. A separate sample preparation document will be provided which describes the process in more detail. Samples collected in any participating sites will be held within the Cambridge Neurosurgical Laboratories, Level 6, A-block, Addenbrooke's Hospital, Hills Road, Cambridge. Blood samples will be stored until they are used for translational research.

Other sites can also participate in the translational research element of STOP'EM, if they wish to and have capacity/funds available to collect and store samples.

Samples are being gifted as part of future research which may include genetic testing for specific biomarkers of inflammation that could have an effect on seizure risk. Separate funding and regulatory approvals will be sought for this future research.

Sub-study 2 (imaging biomarkers) **[mandatory for all sites]**
All participants will undergo an MRI at baseline (pre-operatively) and at ~52 weeks post-operatively, as part of their routine care and follow-up. Images will be pseudo-anonymised and transferred electronically, via the Image Exchange Portal, for central review.

A separate MRI manual will be provided to sites – this will contain imaging sequences and transfer instructions.

The storage of MRIs is not part of the STOP'EM study and is not funded by NIHR as part of NIHR129748.

12 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial. For STOP'EM, data on Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions will be collected

12.1 Terms and Definitions

Adverse Reaction (AR)
Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Serious Adverse Reaction (SAR)
An adverse reaction which meets the definition of serious (see Section 12.3) is a Serious Adverse Reaction. A Serious Adverse Reaction event that has been assessed as 'expected' (see Section 12.6) according to the Reference Safety Information (see below) will remain classified as a Serious Adverse Reaction only, however some Serious Adverse Reactions that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information (RSI)
The information used for assessing whether an adverse reaction is expected (see section 12.6). This is contained in the Summary of Product Characteristics (SmPC) or Investigators Brochure (IB) for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The RSI for this trial is defined in section 12.6.1.

12.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event / reaction is assessed as serious if it:

- Results in death;
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAR);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject

and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

12.3 Severity of Adverse Reactions

All adverse reactions should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below. A distinction is drawn between **serious** and **severe** ARs. Severity is a measure of intensity (see below) whereas seriousness is defined using the criteria in Section 12.2. Hence, a severe AR need not necessarily be a "serious" AR.

Table 2: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.

12.4 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assignment of the causality should be made using the definitions in the table below:

Table 3: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the event should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on known safety profiles of IMP, or SmPC, or sIMPD and known risk profiles of other drugs in the same class. If any doubt about the causality exists the local investigator should inform the LCTC who will notify the Chief Investigator. In the case of discrepant views on

causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA & REC will be informed of both points of view.

12.5 Assessment of "Expectedness"

There is no requirement for a reporting investigator to make an assessment of expectedness. The Chief Investigator for the STOP'EM trial, delegated as the medical reviewer on behalf of sponsor, is responsible for determining whether a safety event is expected or unexpected. However, a Chief Investigator will not assess reports on their own participants; these participant safety reports will be assessed by an alternative Medical Reviewer.

An event will be considered unexpected if it is not listed within the current and approved RSI / protocol for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI / protocol the event should be assessed as unexpected.

12.6.1 Reference Safety Information / Information used to Assess Expectedness

The Reference Safety Information (RSI) for STOP'EM is section 4.8 of the Amarox Levetiracetam 250mg Summary of Product Characteristics (SmPC).

There is no RSI for the placebo. As there are no expected events for the placebo, all events thought to be related to the placebo will be SUSARs.

12.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the "active monitoring" period described below, which meet the definition of serious (see section 12.2) and are recorded for this study, must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in sections 12.9 and 12.10. The same processes established for SARs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from the period of randomisation until completion of IMP course, plus 1 week.

Section 12.7 for more information on reporting pregnancy.

Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).

- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Pregnancy (See section 12.7 for more details)

Do not record:

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery[1]
- Overdose of medication **without signs or symptoms***[2]
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

[1] Cosmetic elective surgery is cited here as example of an event that is not reportable as an AR

[2] Note that although overdose of medication without signs or symptoms may be excluded from AR reporting, it may still require investigation to ensure other protocol and regulatory requirements are met e.g. for IMP management and administration, or to ensure participant safety. If applicable, refer to appropriate part of Treatment section 8.9 (Overdose).

N.B. If overdose occurred **with resulting signs and symptoms that meet the protocol criteria for SAR/SUSAR then they should be reported accordingly (see section 13.1 for more information) and the overdose highlighted to the LCTC team.*

The events above do not need recording as the trial is considered low risk.

12.7 Reporting of Pregnancy

If pregnancy occurs during either the intervention or up to eight weeks after surgery this must be notified to the LCTC using the appropriate CRF within 24 hours of the research team becoming aware. The pregnancy must be followed up by the site research team until outcome and reported to LCTC.

Any pregnancies which result in a safety event assessed as "serious" (e.g. birth defect) must also be reported separately on the appropriate safety event CRFs in accordance with processes described in section 13.1. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

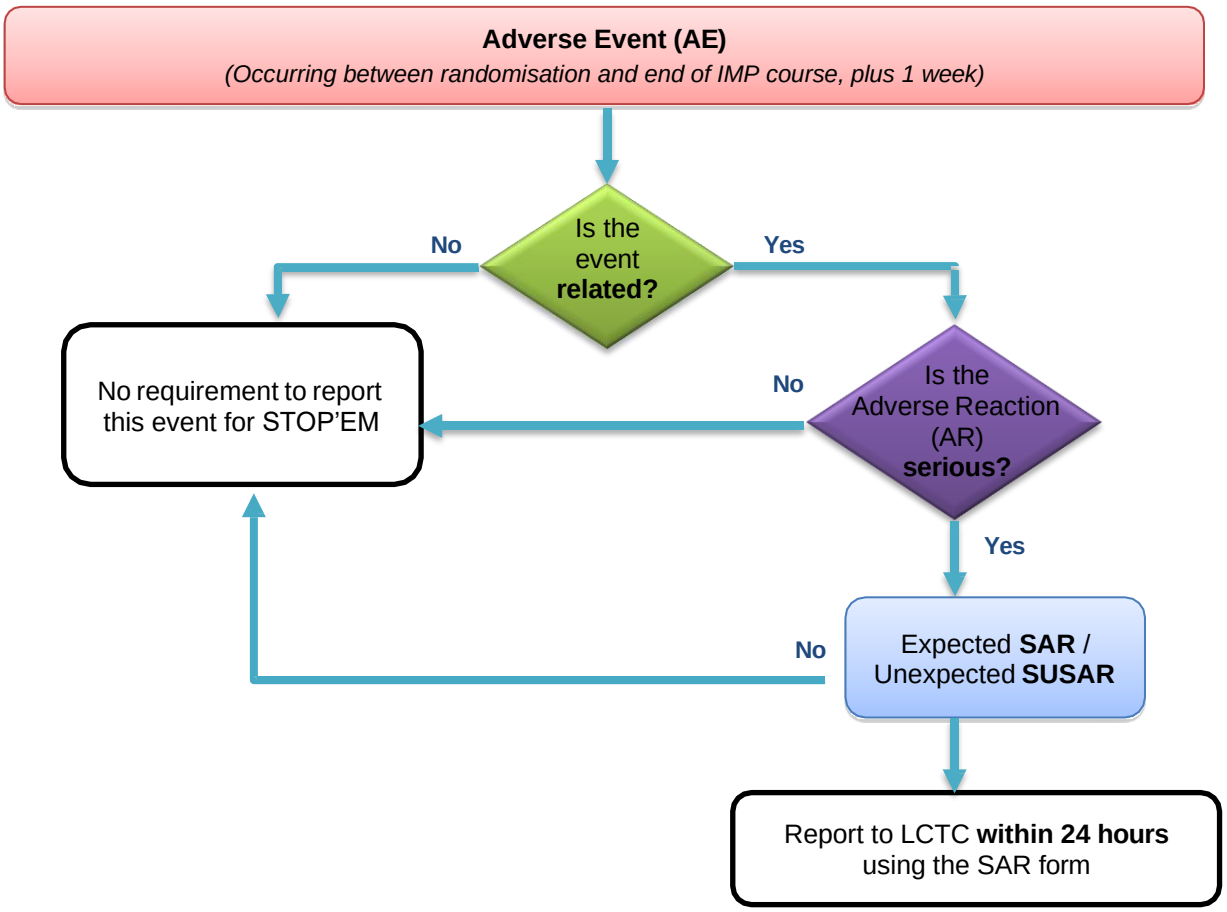
12.8 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate CRF within 24 hours of becoming aware.

12.9 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning adverse reaction reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse reactions.

Flowchart for Site Reporting Requirements of Adverse Reactions



Reporting Safety Events to the LCTC

Safety events which are assessed as "serious" must be recorded in more detail on Serious Safety Event Forms; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded.. Where additional information is received by site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. Serious Safety Event Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the Chief Investigator or Medical Reviewer, and assessed for causality and expectedness.

Follow-up After Adverse Reactions

All reportable adverse reactions should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting "serious" safety reactions, the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

12.10 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events the correct medical terminology **must** be used in accordance with MedDRA.

Safety events which meet the definition of "serious" must be reported in more detail to the LCTC on an SAR form reported **immediately and in no circumstances later than 24 hours from becoming aware** where they will be appropriately processed.

The SAR form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality (relationship to IMP and placebo) must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

The minimum information required for reporting is as follows:

- Valid EudraCT number
- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- One SAR
- One suspect IMP (including active substance name)
- A causality assessment.

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible

thereafter the responsible investigator should check the SAR form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the the site R&D team in accordance with local policy.

REPORTING AN INITIAL OR FOLLOW-UP SAR

The investigator should ensure the actions below are completed for all reportable SARs:

1) Research sites should telephone the appropriate trial co-ordinator / data manager as soon as possible on telephone number **0151 795 1732** to advise that an SAR report has been submitted.
2) **The SAR form should be transferred to the LCTC Central Safety Team via secure email, to LCTCSafe@liverpool.ac.uk, within 24 hours of the local team becoming aware of the event.**
3) The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
4) The participant must be identified by trial randomisation number, age or month and year of birth and initials **only**. The participant's name **should not** be used on any correspondence.
5) SARs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. N.B. Follow-up may continue after completion of protocol treatment if necessary.
    - Follow-up information is noted on a new SAR form to be transferred securely to the LCTC as soon as more information becomes available
    - Tick the appropriate box on the new SAR form to identify the type of report; this is dependent on resolution status of the SAR e.g. follow-up / final.
6) No extra, annotated information and/or copies of anonymised test results should be transmitted unless explicitly requested.

In the event that an SAR is sent electronically & securely but the sender does not receive email confirmation of receipt/download by recipient by the end of the next working day, the sender should make contact with LCTC to ensure the file was received.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

12.11 LCTC Responsibilities

The trial Sponsor, University of Liverpool, have delegated to LCTC the duty of onward reporting of safety events to REC, regulatory authorities, Sponsor. SOPs will be followed to ensure appropriate reporting as detailed below.

All "serious" safety events will be forwarded to the a designated Medical Reviewer by LCTC within 24 hours of receiving the minimum information from site. The Medical Reviewer will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" and "unexpected" will be expedited to REC and MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC first becoming aware of the event.

Additionally, SUSARs will be reported to the trial Sponsor(s) and Principal Investigators of participating sites within agreed timelines.

The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

It is recommended that the events below are considered for reporting in an expedited manner:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the Sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the participants, such as:
  - A SAR which could be associated with the trial procedures and which could modify the conduct of the trial;
  - A significant hazard to the participant population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
  - A major safety finding from a newly completed animal study (such as carcinogenicity).
  - Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same Sponsor;
  - Recommendations of the Independent Data and Safety Monitoring Committee, if any, where relevant for the safety of the participants.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline, and if appropriate, accompanied by a summary of the evolving safety profile of the IMP.

Any concerns raised by the IDSMC/TSC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported and SARs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

Maintenance of Blinding in Adverse Reaction Reporting

Systems for reporting safety events assessed as "related" (e.g. SAR and SUSAR) should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. SAR forms allow reporting investigators to make an assessment of causality without having to unblind the participant; breaking the blind will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant.

Cases that are considered serious, unexpected and related to the intervention (i.e. SUSARs) will have to be unblinded at the LCTC prior to onward reporting. Unblinding procedures are detailed in Section 8.10.

Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of safety events. The LCTC will send annual developmental safety update reports (DSURs)/Annual Progress Reports (APRs) containing a list of all SARs to the IDSMC, MHRA and main REC. If any safety reports identify issues that

have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The LCTC, as delegated by trial Sponsor, will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

12.12 Contact Details and Out-of-hours Medical Cover

As this trial uses an IMP (Levetiracetam) that has well established safety profile, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision other than access to unblinding information as described in section is required for STOP'EM participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

13 STATISTICAL CONSIDERATIONS

13.1 Introduction

A detailed statistical analysis plan[26] will be developed prior to the first meeting of the Independent Data Safety Monitoring Committee requiring unblinding for comparative analyses. The key features of the statistical considerations and planned analyses are provided.

13.2 Sample Size

Sample Size Calculation

The proportion of participants with seizure occurrence at 12 months is 12.3%[3]. A 50% reduction is clinically beneficial. A two group χ^2 test with a 5% two-sided significance level will have 90% power to detect the difference between a Group 1 proportion of 0.12 and a Group 2 proportion of 0.06 when the sample size in each group is 477. Allowing for 5% dropout a total of 1004 participants will be recruited.

Assuming a conservative recruitment rate of 1.2 participants per month and site, a four-year recruitment period is required allowing for staggered site opening and a conservative estimate of eligibility and consent.

Feasability of Sample Size

Based on a large systematic review and meta-analysis the 12-month post-operative seizure rate is 12.3%[3] and in consultation with patients a 50% reduction was considered clinically beneficial.

There are 1600 operated meningioma per year in the UK and 85-90% are supratentorial (n=1360). 70% are seizure naive (n=952) and are managed across adult neurosurgery units.

Our survey data shows that surgeons who are regular or occasional users of prophylaxis consider midline shift in 38% of cases, oedema in 58% of cases and convexity/parasagittal location in 24% of cases. Our survey data also showed that the same surgeons reported greater uncertainty and willingness to participate in the trial (85% will participate) compared to 'never users' of prophylaxis (63% will participate). We have assumed a consent rate of 70% (based on our experience in previous neurosurgery trials), which allows for clinical and patient preferences regarding participation. This would yield a maximum of 315 randomised participants / year once all sites are open. This assumes patients meet all eligibility criteria, with all potential participants approached. We have therefore used a conservative average recruitment rate of 1.2 participants per month and site.

13.3 Method of Randomisation

Allocation Sequence Generation

Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team at site. Allocation concealment will be ensured as the service will not release the randomisation code until all eligibility criteria are satisfied; this takes place after all baseline measurements have been completed.

Randomisation will use minimisation with a probabilistic element. To reduce any predictability, the factors used within the minimisation algorithm are stored confidentially with restricted access.

13.4 Blinding Considerations

Details regarding blinding are provided in section 6.1.

13.5 Interim Analyses

The trial will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) who will assess the trial data and take into account the current world-wide evidence. The IDSMC members will comply with a trial-specific IDSMC charter.

Analyses of the accumulating data will be performed at regular intervals for review by the IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to make recommendations to the Trial Steering Committee on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

13.6 Analysis Plan

All analyses will be conducted using the intention to treat principle with a 5% level of statistical significance and 95% confidence intervals. A full and detailed statistical analysis plan will be developed prior to the first IDSMC using unblinded data. The primary outcome, and other binary outcomes, will be analysed using logistic regression adjusted for factors included within randomisation process. Time to event outcomes will be analysed using Cox Proportional Hazards adjusting for randomisation factors. Quality of life scores will be analysed using analysis of covariance adjusted for baseline score and randomisation factors. All data will be monitored throughout. Reasons for missing data or participant withdrawals will be collected and used to inform any statistical approach to missing data. Such methods will be fully described in the SAP.

Health economic analysis

The health economic analysis will adopt the perspective of the NHS and PSS and a 12-month time horizon. Costs will include those of the surgery, antiepileptic drugs, duration of intensive care stay and hospital admission and contact with health professionals. Hospital resource use will be estimated from patient-level Hospital Episode Statistics (HES) data obtained from NHS Digital for England. Data on outpatient, inpatient, critical care and A&E attendances will be requested for the financial years commencing 6 months before the start of the study and covering the duration of the study. Participants will be fully and unambiguously informed as to the transfer of any personal data associated with obtaining and processing their HES data and will

agree to these processes by signing the mandatory statement on the consent form. Participants will explicitly be made aware that they have the right to withdraw consent, and how to go about withdrawing their consent, for disclosure of HES data. Participant information (postcode, date of birth, NHS number and randomisation number) will be securely transferred to authorised personnel at NHS Digital. Anonymised and encrypted HES data will be transferred to the Centre for Health Economics and Medicines Evaluation (CHEME), Bangor University via a secure link and stored at Bangor University in accordance with Data Sharing Agreements. The only identifier present in the HES datasets will be the trial randomisation identifier, and health economists at CHEME will not have any access to keys linking this to participants' personal data. Electronic HES records will be stored on secure Bangor University computer servers which meet NHS data security standards. Access will be restricted only to health economists working on the trial.

Administrative data on hospital episodes will be accessed from Patient Linked Information Costing Systems (PLICS), and equivalents in Wales and Scotland. Responsibility for the PLICS data collection and anonymization will rest with the site research nurse who will supply their site Finance Departments with the necessary details to ensure only information on consented participating patients are provided. It is the responsibility of the site Finance Departments to provide the site research nurses with the data in a timely fashion and should the site research nurse so request, to ensure all patient identifying data have been replaced with the patient trial number. Pseudo-anonymised PLICS data will be transferred securely from each site to Bangor University for analysis. LCTC will provide instructions for this transfer.

Episodes of care in ICU and HDU will be recorded in case report forms. Patients' use of primary care services and personal social services will be recorded in resource use questionnaires administered by research nurses at baseline (to ask about the preceding 3 months), and at scheduled follow-up visits. The development of the resource use questionnaire will be informed by existing questionnaires catalogued in the Database of Instruments for Resource Use Measurement[27], and include the core items for standardised resource use measurement[28]. Unit costs will be obtained from standard sources such as NHS reference Health Resource Group tariffs[29], Unit Costs of Health and Social Care[30], and the British National Formulary for medicines. A wider perspective will be analysed (secondary analysis) 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.

The primary health outcome for the economic analysis will be the QALY, based on face-to-face administrations of the EQ-5D-5L questionnaire at baseline and post-operatively at each scheduled follow-up visit (4-6 weeks, 3 & 12 months). Both the patient, and patient proxy (version 1 for carers), of the EQ-5D-5L will be used. The 5L tariff scores will be used to estimate utilities, using NICE's preferred methods at the time of analysis.

For each participant, total costs, and QALYs (estimated by the area under the curve method) will be calculated, and adjusted for baseline values[31]. No discounting will be necessary given the 1-year time horizon. Methods for multiple imputation will be employed to account for data which may be assumed to be missing at random[32]. The incremental cost-effectiveness ratio will be computed and compared with threshold values (NICE £20,000 to £30,000 per QALY gained)[33]. Extensive sensitivity and scenario analyses will be performed, and the joint uncertainty in costs and benefits considered through the application of bootstrapping to generate cost effectiveness acceptability curves[34]. Full details of the economic analysis will be prepared for the Health Economic Analysis Plan.

14 DATA MANAGEMENT AND TRIAL MONITORING

For the STOP'EM trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

14.1 Source Documents

The case report form (CRF) will be considered the source document for data where no prior record exists and which is recorded directly in the bespoke CRF. A STOP'EM source document list will be produced for each site to be kept in the Investigator Site File (ISF).

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

14.2 Data Collection Methods

eCRF access will be provided to sites for local completion by members of the research team trained and delegated the duty. Study staff named at each site will enter data into the STOP'EM database. Training will be provided prior to any data entry. The eCRF is the primary data collection instrument for the study so all data requested on the eCRF **must** be recorded in the medical notes, and all missing data must be explained.

SAR forms and pregnancy forms will be paper or eCRFs. Any corrections to these should be made in accordance with GCP. These forms will be scanned to LCTC, and the original wet-ink copies will then be posted to LCTC.

Where participants attend site for trial visits, paper questionnaires can be used. Questionnaires are a source document. Sites should enter data from the paper questionnaires into the STOP'EM database and retain the wet-ink completed questionnaires in their site file.

14.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted inaccordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be informed by the trial risk assessment. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

Central Monitoring

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database which will allow for checks for missing or unusual values (range checks) at the point of data entry. Additional complex checks will be undertaken by the statisctical team periodically. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be raised as data queries within the trial database. Sites will respond to the queries within the database by updating the data or providing an explanation to the discrepancies.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

14.4 Risk Assessment

A study specific risk assessment will be performed and reviewed by representatives of the Sponsor, LCTC and the Chief Investigator or designee. The risk assessment will be compliant with LCTC SOPs and will form the basis of the monitoring plans and audit plans.

14.5 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial randomisation number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

HES data, obtained from NHS Digital, will be pseudo-anonymised using the trial randomisation number and securely sent to Bangor University for analysis. LCTC will transfer identifiable data to NHS Digital for the purpose of obtaining linked patient routine NHS data.

N.B. Consent forms must be transferred separately to any other trial documentation. Ensure the pseudonymisaiton of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool/Bangor University is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

14.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management and monitoring Plans.

14.7 Records Retention

The retention period for the STOP'EM data and information is 15 years from the official End of Trial date (except raw source HES data from NHS Digital, that will only be retained for the duration of the Data Sharing Agreements) (defined in section 10.10 above).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File, the applicable participant medical records and Pharmacy Site File, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the Sponsor / LCTC.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, IMP manufacturers and distributors, third-party vendors providing randomisation and IMP allocation systems, etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Statement of Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended and will abide by the appropriate principles of the World Medical Association Declaration of Helsinki. This trial has been designed to be as pragmatic as possible.

15.2 Ethical Considerations

The trial will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). Before the trial can commence, all required approvals will be in place. The protocoand relevant documents will undergo an ethical review by an independent Research Ethics Committee (REC) and any conditions of approvals will be met.

15.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical e.g. MHRA and REC requirements are handled based on their nature and severity.

Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by the LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

16 INDEMNITY

University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

17 PUBLICATION AND DISSEMINATION

17.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s), Trial Manager(s) and Health Economics(s) involved as a minimum.

All involved clinicians / nurses at each participating site will be listed under a group authorship as 'STOP'EM Consortium' in the final publication and will be named individually for pubmed indexing. The ISRCTN number allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the STOP'EM Consortium which will also be named at the manuscript head.

17.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the regulatory bodies (MHRA and REC) and funder (NIHR HTA). The results of STOP'EM will be published regardless of the magnitude or direction of effect.

Results will be shared with the participating study team, professional bodies and charities. It is anticipated as Meningioma is the most common brain tumour, the results of this study will also lead to the creation of guidelines for seizure prophylaxis in meningioma surgery that will inform national and international neurosurgery practice.

17.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by an internal committee at the LCTC and discussed with the Chief Investigator in accordance with the LCTC policy on data sharing.

18 CHRONOLOGY OF PROTOCOL AMENDMENTS

18.1 Version 2.0 (28/03/2023)

Amendments were required to protocol version 1.0 (15/09/2022) following receipt of a grounds for non-acceptance letter (with right to amend request) from the Regulatory Authorities (Combined Review by MHRA, REC & HRA).

Section Number	Section Title	Summary of Changes
N/A	N/A	Protocol version number and date updated.
Front page	N/A	CTA and REC references added.
1	Table of Contents	Table of Contents updated to reflect change to section 18.
3 and 7.2	Exclusion criteria	Exclusion criterion 5 amended – CKD 3 no longer excluded; only CKD 4-5 to be excluded. New exclusion criteria added: 7. Known hypersensitivity to levetiracetam, other pyrrolidone derivatives or any of the excipients 8. Actively breastfeeding 9. Weigh below 50kg (if aged 16 or 17 years)
5.3	Risk and Benefits	Trial category based upon potential risk associated with the IMP amended from Type A to Type B, following feedback from MHRA.
6.4	Internal Pilot (Stage 2 – 24 months from recruitment start)	Text added to clarify that sample size assumptions refer to the control group event rate.
10.3	Eligibility Assessment and Confirmation	Special note added highlighting that participants with prolonged QT interval (QT interval >500 milliseconds) will be managed as per local routine clinical pathways.
10.5	Randomisation Process	Text added to clarify timing of eligibility and baseline assessments in relation to time randomisation and surgery.
10.7	Schedule for Assessments and Follow-up	Text added at follow-up 1 and 2 highlighting that checks on suicidal ideation and psychosis should be made, and managed clinically as per routine practice.
13.3	Method of randomisation	Text added to clarify method of randomisation.
18	Chronology of Protocol Amendments	List of changes made to protocol v1.0 to form v2.0 added.

18.2 Version 1.0 (15/09/2022)

Original version submitted for Regulatory review.

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20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or Ethical review are submitted as separate version controlled documents.

21 DEFINITIONS

21.1 Definition of seizure

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

1. Focal seizure with retained awareness:
   a) with motor symptoms: focal motor movements, versive/postural movements
   b) with sensory symptoms: olfactory sensations
   c) with autonomic signs
   d) with psychic symptoms (sudden reversible loss of expressive/receptive speech)

2. Focal seizures with altered awareness:
   a) with impairment of consciousness only
   b) with impairment of consciousness plus automatisms (lip smacking, fumbling)
   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 jerking of one side of the face or limb(s) on one side
      - Turning the head to one side

3. Focal to bilateral convulsive seizures:
   a) Unconsciousness with generalised jerking

21.2 Karnofsky performance score (KPS)

The Karnofsky performance score[35]:

KPS score	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary: active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

KPS = Karnofsky Performance Score.