Pharmacological management of seizures post traumatic brain injury (MAST trial).

MAST trial: Anti-epileptic drug use following brain injury

CLINICAL TRIAL PROTOCOL

Protocol version: 2.0

Protocol date: 18.12.2020

Clinical Trial Protocol

Trial Title:	Pharmacological management of seizures post traumatic brain injury (MAST trial)
Protocol Number:	MAST01
EudraCT Number:	2020-000282-16
ISRCTN Number:	ISRCTN13200656
Investigational Product:	Levetiracetam, Phenytoin
Protocol Version:	2.0

Chief Investigator:	Professor Peter Hutchinson
CI Address:	University of Cambridge Dept of Clinical Neurosciences Division of Neurosurgery Box 167 Cambridge Biomedical Campus Cambridge CB2 0QQ
Telephone:	+44 (0)1223 336946
Co-ordinating Centre:	Cambridge Clinical Trials Unit (CCTU) Coton House, Level 6, Box 401, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ Telephone: + 44 (0)1223 256624 Email:samantha.lawes@addenbrookes.nhs.uk
Trial Sponsor:	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
SAE Reporting:	Cambridge Clinical Trials Unit (CCTU) Clinical Trial Coordinator (CTC): Dr Samantha Lawes Telephone: + 44 (0)1223 256624 Email:addtr.mast@nhs.net
Funder:	NIHR Health Technology Assessment Programme

1 Protocol Signatures:

I give my approval for the attached protocol entitled Pharmacological management of seizures post traumatic brain injury (MAST trial) dated.....

Chief Investigator

Name: Professor Peter Hutchinson

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled "Pharmacological management of seizures post traumatic brain injury (MAST trial)" dated ..... and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name:

Signature: _____

Date: _____

2 Trial Management Committee(s) and Protocol Contributors

Chief Investigator
Professor Peter Hutchinson
Professor of Neurosurgery & Honorary Consultant Neurosurgeon
University of Cambridge & Cambridge University Hospitals NHS Foundation Trust
Telephone: + 44 (0)1223 336946
Email: pjah2@cam.ac.uk

Clinical Trial Coordinator (CTC)
Dr Samantha Lawes
Cambridge Clinical Trials Unit
Telephone: + 44 (0)1223 256624
Email: samantha.lawes@addenbrookes.nhs.uk
OR samantha.lawes@nhs.net

Trial Statistician
Dr Simon Bond
Senior Statistician
Cambridge Clinical Trials Unit
Telephone: + 44 (0)1223 596475
Email: simon.bond@addenbrookes.nhs.uk

Independent TSC Chair
Professor Anthony Bell
Professor of Neurosurgery
St George's University of London
Telephone +44(0) 2087254179
Email: neurosur@sgul.ac.uk

Independent DMC Chair
Prof Martin Smith
Professor in Neurocritical Care
University College London Hospitals
Telephone +44 (0)2078298711
Email: martin.smith@uclh.nhs.uk

Clinical Trial Pharmacist
Dr Lynne Whitehead
Clinical Trials Pharmacist
Cambridge University Hospitals NHS Foundation Trust
Telephone: +44 (0)1223 216057
Email: lynne.whitehead@addenbrookes.nhs.uk

Trainee Representatives
Mr Angelos Kolias
Neurosurgical Registrar
University of Cambridge & Cambridge University Hospitals NHS Foundation Trust
Telephone: + 44 (0)1223 746452
Email: ak721@cam.ac.uk

Mr Edoardo Viaroli
Clinical Fellow Neurosurgery
Cambridge University Hospitals NHS Foundation Trust

Telephone: + 44 (0)1223 746452
Email: edoardo.viaroli@addenbrookes.nhs.uk

Dr Harry Mee
Clinical Researcher
University of Cambridge & Cambridge University Hospitals NHS Foundation Trust
Telephone: +44(0)1223 256201
Email: hwjm2@cam.ac.uk

Society of British Neurological Surgeons Research Development & Clinical Trials Manager
Mrs Carole Turner
University of Cambridge
Telephone: + 44 (0)1223 217205
Email: clt29@medschl.cam.ac.uk

Protocol Contributors
Professor Anthony Marson
Professor of Neurology
University of Liverpool,
Telephone:+ 44 (0)151 529 5705
Email: a.g.marson@liverpool.ac.uk

Professor John Duncan
Professor of Clinical Neurology
UCL Institute of Neurology
Telephone: +44 (0)3448 8613
Email: j.duncan@ucl.ac.uk

Professor Mark Richardson
Vice Dean for Neurosciences
Kings College Hospital NHS Foundation Trust
Telephone: + 44(0)2078365454
Email: m.richardson@ion.ucl.ac.uk

Professor Fiona Lecky
Clinical Professor in Emergency Medicine
University of Sheffield
Telephone: 0114 2220834
Email: f.e.lecky@sheffield.ac.uk

Dr Tim Ham
Consultant Neurologist
Cambridge University Hospitals NHS Foundation Trust
Telephone: + 44 (0)1223 245151
Email: hamt@addenbrookes.nhs.uk

Dr Fahim Anwar
Consultant in Rehabilitation Medicine
Cambridge University Hospitals NHS Foundation Trust
Telephone: 01223 245151
Email: fahim.anwar@addenbrookes.nhs.uk

Professor Mark Wilson

Clinical Professor and Pre-hospital Care Specialist
Imperial College of Science, Technology and Medicine
Telephone: + 44 (0)20 3312 6666
Email: acutebrain@gmail.com

Professor Garry Barton
Professor of Health Economics
Norwich Clinical Trials Unit
Telephone: +44(0)1603 591936
Email: g.barton@uea.ac.uk

Dr Ari Ercole
Lecturer and Consultant Anaesthetist
Cambridge University Hospitals NHS Foundation Trust
Telephone: 01223 245151
Email: ae105@cam.ac.uk

Dr David Christmas
Consultant Psychiatrist
Cambridge University Hospitals NHS Foundation Trust
Telephone: 01223 245151
Email: David.Christmas@cpft.nhs.uk

Professor Antonio Belli
Professor of Trauma Neurosurgery
University of Birmingham
Telephone: +44(0)1214 144497
Email: a.belli@bham.ac.uk

Professor Garth Cruickshank
Professor of Neurosurgery
University of Birmingham
Telephone: 0121 414 3344
Email: g.s.cruickshank@bham.ac.uk

Patient Representatives
Mr James Piercy
Patient Representative
Email: mailthepiercy@gmail.com

Table of Contents

3 Abbreviations

AE/AR	Adverse event/Adverse Reaction
AED	Anti-Epileptic Drug
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CRF	Case Report Form
CTC	Clinical Trial Co-ordinator (Central)
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EQ-5D-5L	Health related quality of life assessment (based on 5 dimensions each of which have 5 levels)
GP	General Practitioner
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GOS	Glasgow Outcome Scale
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICF	Informed Consent Form
IHP	Independent Healthcare Professional
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non Investigational Medicinal Product
NSI	Neurobehavioural Symptom Inventory
NSU	Neurosurgical unit
PIS	Participant Information Sheet
PSS	Personal Social Services
PTS	Post-Traumatic Seizures
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic brain injury
TMG	Trial Management Group
TSC	Trial Steering Committee

4 Trial Synopsis

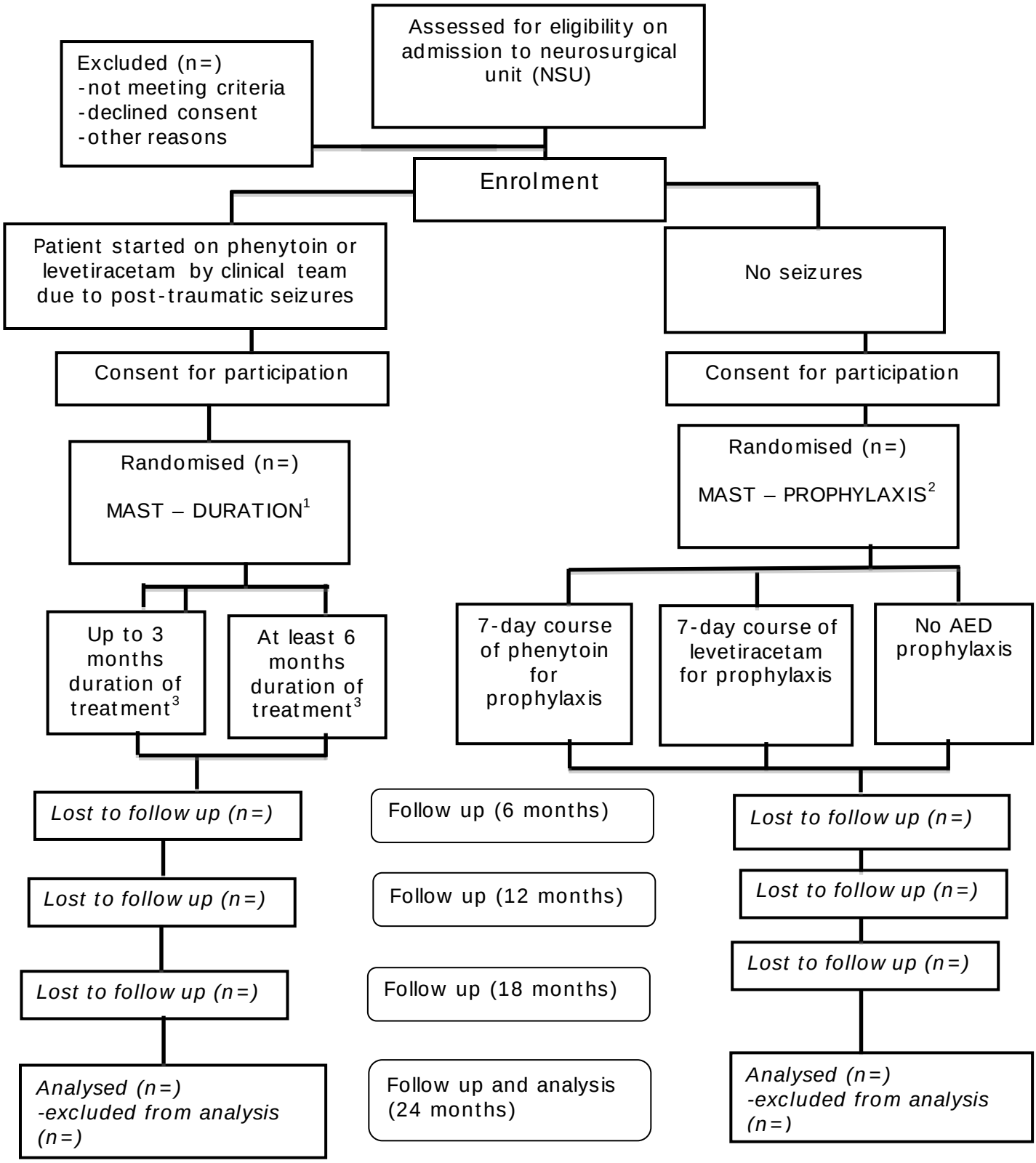
Title of clinical trial	Pharmacological management of seizures post traumatic brain injury
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
EudraCT number	2020-000282-16
Medical condition or disease under investigation	Seizures post-traumatic brain injury
Purpose of clinical trial	To assess 1. Anti-epileptic drug (AED) prophylaxis following traumatic brain injury (TBI) (MAST-PROPHYLAXIS) 2. Duration of AED treatment following post-traumatic seizure(s) (PTS) (MAST-DURATION) This will be assessed by conducting 2 parallel but independent trials. Eligibility to enter either trial will be dependent on whether an early seizure has occurred.
Primary objective	***MAST_PROPHYLAXIS:*** To determine the comparative clinical effectiveness (absolute difference in the rate of PTS within the first 2 weeks post-TBI) of a 7-day course of phenytoin or levetiracetam, used as seizure prophylaxis, versus no AED for TBI patients ***MAST-DURATION:*** To determine the comparative clinical effectiveness (absolute difference in the rate of late PTS within 24 months post-TBI) of a longer course of phenytoin or levetiracetam (at least 6 months) versus a shorter course (up to 3 months) for TBI patients with early seizures
Secondary objective (s)	***MAST-PROPHYLAXIS:*** 1. Compare the rate of PTS within 24 months post-TBI 2. Compare outcomes (extended Glasgow Outcome Scale), cognitive function (Neurobehavioural Symptom Inventory), quality of life (EQ-5D-5L), and adverse events (Liverpool Adverse Events Profile) at 6, 12, 18 and 24 months, between the three arms. 3. Undertake a detailed economic evaluation. 4. To compare the frequency of PTS between the three arms. 5. Mortality at 6, 12, 18 and 24 months. 6. Adverse events of special interest during treatment. ***MAST-DURATION:*** 1. Compare outcomes (extended Glasgow Outcome Scale), cognitive function

	(Neurobehavioural Symptom Inventory), quality of life (EQ-5D-5L), and adverse events (Liverpool Adverse Events Profile) at 6, 12, 18 and 24 months, between the two arms. 2. Undertake a detailed economic evaluation. 3. To compare the frequency of PTS between the two arms. 4. Mortality at 6, 12, 18 and 24 months. 5. Adverse events of special interest during treatment.
Trial Design	***MAST-PROPHYLAXIS***: Phase 3, randomised multi-centre, pragmatic, parallel group trial. ***MAST-DURATION***: Phase 3, randomised multicentre, pragmatic, parallel group trial Both studies will start with an internal pilot study.
Trial Outcome Measures	**Primary outcome measure:** • MAST-PROPHYLAXIS: Occurrence of PTS within 2 weeks after TBI. • MAST-DURATION: Occurrence of late PTS within 24 months after TBI. **Secondary outcome measures:** • PTS up to 2 years (MAST-PROPHYLAXIS only) • Extended Glasgow Outcome Scale, Neurobehavioural Symptom Inventory, quality of life (EQ-5D-5L), and Liverpool Adverse Events Profile at 6, 12, 18 and 24 months. • Economic evaluation • Frequency of PTS • Mortality at 6, 12, 18 and 24 months. • Adverse events of special interest during treatment.
Sample Size	Recruitment of: **MAST-PROPHYLAXIS:** 1221 patients in total (130 in an internal pilot) **MAST-DURATION**: 428 patients in total (50 in an internal pilot)
Summary of eligibility criteria	**MAST-PROPHYLAXIS** Inclusion Criteria: • Patients aged ≥10 years, with TBI managed in an NSU without an acute symptomatic seizure • Patient or Legal Representative is willing and able to provide informed consent or in the absence of a legal representative, an Independent Healthcare Professional provides authorisation for patient enrolment Exclusion Criteria • Post-traumatic seizures

	• Un-survivable injury • Previous history of epilepsy • Patients who are on an AED pre-TBI • Pregnancy or breastfeeding • Any hypersensitivity to study drug (or hydantoins or pyrrolidone derivatives) or any of its excipients • Time interval from the time of admission to NSU to randomisation exceeds 48 hours **MAST-DURATION** Inclusion Criteria: • Patients aged ≥10 years with TBI managed in an NSU who have started on phenytoin or levetiracetam due to an acute symptomatic seizure during acute hospitalisation • Patient or Legal Representative is willing and able to provide informed consent or in the absence of a legal representative, an Independent Healthcare Professional provides authorisation for patient enrolment Exclusion Criteria: • Un-survivable injury • Previous history of epilepsy • Patients who are on an AED pre-TBI • Patient who has been clinically prescribed an AED to treat PTS (other than phenytoin or levetiracetam) since current admission • Any hypersensitivity to study drug selected or any of its excipients
Investigational medicinal product and dosage	Phenytoin as prescribed clinically Levetiracetam as prescribed clinically In MAST-DURATION the choice of AED (phenytoin or levetiracetam) will be at the discretion of local clinical teams.
Route(s) of administration	Oral, nasogastric tube, IV
Maximum duration of treatment of a participant	**MAST-PROPHYLAXIS:** 7 days **MAST-DURATION**: Up to 24 months dependent on clinical need
Procedures: Screening & enrolment	Review of clinical situation (TBI patients) will be undertaken by a member of the clinical team. Informed consent will be obtained from the patient, patient's representative (if the patient lacks capacity) or by agreement with an independent clinician.

Procedures: Baseline	• Inclusion/exclusion criteria review • Informed consent process followed and consent or authorisation for enrolment obtained. *Standard of Care* • Patient medical history (including co-morbidities and relevant medications) and patient demography • Neurological status • Imaging modality and date of examination • Presence of PTS during the treatment period / after the prophylaxis
Procedures: Treatment period	• Standard clinical monitoring to discharge • Follow up at 14 days (PROPHYLAXIS) • Follow up at 6 months (+/- 8 weeks) • Follow up at 12 months (+/- 8 weeks) • Follow up at 18 months (+/- 8 weeks) • Follow up at 24 months (+/- 8 weeks)
Procedures: End of trial	The date of the last patient's final assessment/loss to follow-up.
Procedures for safety monitoring during trial	All results will be forwarded to the Data Monitoring Committee (DMC) who will address safety issues. Any significant adverse results will be reported to the DMC via the Trial Coordinating Centre (CCTU). Onward reporting to the TSC and Sponsor.
Criteria for withdrawal of participants	• SUSAR • Withdrawal from treatment - participants may voluntarily withdraw from treatment for any reason at any time, but continue to provide follow-up data • Withdrawal from trial - participants may voluntarily withdraw from treatment for any reason at any time, and also withdraw from data collection • Patients will be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason
Randomisation	Randomisation in MAST-PROPHYLAXIS will occur within 48 hours from admission to NSU. Randomisation in MAST-DURATION can occur at any time point during acute hospitalisation in the NSU as long as the patient has been started on Phenytoin or Levetiracetam due to post-traumatic seizures.

5 Figure 1: Trial Flow Chart



6 Introduction

6.1 Background

Traumatic brain injury (TBI) is an alteration in brain function or other evidence of brain pathology, caused by an external force [1].It is a major public health problem that can result in physical, cognitive, functional and psychosocial disability [2, 10]. The majority of patients who have a TBI do not need to stay in hospital. However, approximately 9,000 patients require admission to a specialist hospital each year in the UK, as their injury is more serious [3]. Post-traumatic seizures (PTS) are well recognised following TBI [2,4,8,12]. They are classified as acute symptomatic or provoked (within 7 days post-TBI) or late (after 7 days). Seizures during acute hospitalisation can lead to significant derangement of brain physiology and can even lead to brain herniation and death. Additionally, PTS during acute hospitalisation have been shown to be an independent risk factor for PTS within 12 and 24 months following TBI [4]. Late PTS within 24 months can have a negative impact on quality of life, return to work, return to driving, and can even result in death.

Current international guidelines for traumatic brain injury (TBI) [8] recommend the use of phenytoin for the prevention of early PTS when the benefits are thought to outweigh the risks, however the inadequacy of current evidence underpins this guidance. In practice alternative antiepileptic drugs (AEDs) such as levetiracetam and valproate are being used clinically as they are believed to have a more favourable risk profile. This is despite there being insufficient evidence to support their efficacy, or indeed that of phenytoin. In fact at the moment it remains unclear which AED treatment is more appropriate in patients with PTS and for how long patients should be treated. It is also unclear if prophylaxis for PTS following TBI is clinically effective, which patients might benefit from this treatment and for how long the drug should be given. The only evidence currently available dates back to 1990 when Temkin et al. showed a reduced incidence of rate of early seizures from 14.2% to 3.6% after administration of phenytoin [5].

Acute symptomatic seizures are potentially harmful. Recurrent PTS after TBI can negatively impact on quality of life, return to work/driving, and can even lead to death. AEDs are the mainstay of treatment for patients with PTS but are associated with side effects that, if serious, can negatively impact on quality of life, cognition, and general health [3,4,10,12]. Patients with acute symptomatic seizures are typically started on an AED in order to prevent seizure recurrence. The optimal duration of treatment remains unclear. MAST-DURATION will compare a long course of AED (at least 6 months) vs a shorter course (up to 3 months). The duration of AED treatment in the two arms was determined on the basis of our recent UK-wide survey [12] and consensus among the multidisciplinary group of co-applicants. Additionally, we decided to include only patients who have been started on phenytoin or levetiracetam by the clinical teams on the basis of i) feedback by the HTA funding committee during assessment of the stage 1 application and ii) the fact that these two AEDs are used by over 90% of clinicians who completed our survey. Our survey [12] was completed by 117 respondents, predominantly neurosurgeons (76%) from 30 (of 32) trauma-receiving hospitals in the UK and Ireland. The main results were: 53% of respondents do not routinely use seizure prophylaxis, but 38% of those that do, prescribe prophylaxis for one week. 60% feel there is uncertainty regarding the use of seizure prophylaxis, and 71% would participate in further research to address this question. 62% of respondents use levetiracetam for treatment of seizures during the acute phase, and 42% continued for a total of 3 months. Overall, 90% were uncertain about the duration of treatment for seizures, and 78% would participate in further research to address this question. Our survey also showed that almost half of the respondents use a short AED course as seizure prophylaxis, even though this practice is only supported by low-quality evidence [7]. MAST-PROPHYLAXIS will compare a 7-day course of AED (either levetiracetam or phenytoin) versus no AED.

Phenytoin is an AED that was introduced in the 1930's and now is still widely used in clinical

practice. Its main mechanism of action is by blocking voltage-dependent sodium channels [14] and it can be administered both orally or intravenously. Due to its unpredicatable pharmacokinetics, drug interactions and competition for protein binding, in acute situations, such as seizures following TBI, blood plasma levels should be monitored initially until stability and then a continued dose maintained. Plasma levels are not routinely checked after this unless further seizures occur or if required for other clinical reasons, then doses would be adjusted as required. Side effects include thrombophlebitis, extravasation injury and arrhythmia when given intravenously and include gingival hypertrophy, body hair increase, rash and folic acid depletion in oral or intravenous preparations

Levetiracetam has efficacy against focal onset seizures and its main mechanism of action is thought to be via binding to the SV2 synaptic vesicle [17]. Due to its small potential for pharmacokinetic interactions with other drugs, the fact it does not require a titration period [15] or routine monitoring of plasma levels it has become a very common AED in clinical practice. In the acute setting a loading dose can be administered. Side effects include drowsiness, mood alterations and some longer term behavioral disturbances [16]. Side effects and adherence will be monitored and recorded during the follow up period in both studies. A recommended dosing strategy will be outlined in the protocol to include loading doses and plasma monitoring as required.

Mechanism of Action

Phenytoin

The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures. The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 halflives) after initiation of therapy with recommended doses of 300 mg/day. When serum level determinations are necessary, they should be obtained at least 5–7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For Dilantin capsules, peak serum levels occur 4 to 12 hours after administration. Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but more importantly by tubular secretion. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Levetiracetam

The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures [6]. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepinesbenzodiazepin es, GABA (gammaaminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, in vitro studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, in vitro studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells. A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their anti-seizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

6.2 Clinical Data

Levetiractetam

Pharmacokinetics

The pharmacokinetics of levetiracetam has been studied in healthy adult subjects, adults and paediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment. Levetiracetam is not licensed for the treatment of PTS in adults or children, although is routinely given in practice. It is indicated as monotherapy in the treatment of seizures in adults >16 years with newly diagnosed epilepsy.

Absorption and distribution
Levetiracetam is rapidly and almost completely absorbed after oral administration. Levetiracetam tablets and oral solutions are bioequivalent. The pharmacokinetics are linear and time-invariant, with low intra- and inter-subject variability. The extent of bioavailability of levetiracetam is not affected by food.

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases Cmax by 20% and delays Tmax by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500- 5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism and elimination

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function.

Pharmacokinetic interactions

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above Cmax levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Phenytoin

Phenytoin is an antiepileptic drug which is licensed in the prevention and treatment of seizures in adults and children, during and following neurosurgery and/or severe head injury and epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to

stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centres responsible for the tonic phase of tonic-clonic (grand mal) seizures.

Absorption and distribution

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 halflives) after initiation of therapy with recommended doses of 300 mg/day. When serum level determinations are necessary, they should be obtained at least 5–7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For Dilantin capsules, peak serum levels occur 4 to 12 hours after administration. Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

Metabolism and elimination

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but more importantly by tubular secretion. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Pharmacokinetic interactions

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

7 Rationale for Trial

The overall aim of the MAST trial is to define best practice in the use of anti-epileptic drugs for patients following a traumatic brain injury.

The MAST-PROPHYLAXIS trial has been designed to assess the clinical effectiveness of a short course of phenytoin or levetiracetam, used as seizure prophylaxis.

The MAST-DURATION trial has been designed to determine the clinical effectiveness of a short course versus a longer course of AEDs in the prevention of further seizures.

The two closely related clinical trials will be conducted, in parallel but independent of each other.

The choice and duration of the trial drugs, phenytoin and levetiracetam, are reflective of a recent survey carried out in neurosurgical centres around the UK.

MAST-PROPHYLAXIS
P Patients aged ≥10 admitted to the NSU post TBI who have not had a seizure.
I The intervention is phenytoin OR levetiracetam for 7 days
C No AED administered
O Outcome is evidence of PTS within 2 weeks of TBI

MAST-DURATION:
P Patients aged ≥10 admitted to the NSU who have been started on an AED (phenytoin or levetiracetam accepted), due to early symptomatic seizures after TBI (within first 7 days following trauma).
I The intervention is an AED administered for at least six months
C The comparator is an AED administered for up to 3 months
O Outcome is evidence of PTS at 2 years from TBI

8 Trial Design

8.1 Statement of Design

MAST-PROPHYLAXIS: A multi-centre, pragmatic, three arm, open label, randomised trial aiming to determine the comparative clinical and cost-effectiveness of a 7-day course of phenytoin or levetiracetam, used as seizure prophylaxis, versus no AED for TBI patients.

MAST-DURATION: A multi-centre, pragmatic, two arm, parallel, open label, randomised trial aiming to determine the comparative clinical and cost-effectiveness of a longer course of phenytoin or levetiracetam (at least 6 months post-TBI) versus a shorter course (up to 3 months) for TBI patients with early seizures (within first 7 days following trauma).

Both studies will be preceded by an internal pilot in order to confirm recruitment, randomisation, treatment, and follow-up assessments. We have defined robust progression criteria, on the basis of recently published recommendations [13]. On reaching, the pre-defined success criteria, the internal pilot studies will run seamlessly into the main trials.

8.2 Number of Centres

Stage 1 will take place in approximately 10 centres in the UK, to ensure feasibility. If successful, stage 2 will follow and will encompass, where possible, all remaining neurosurgical centres in the UK.

8.3 Number of Participants

MAST-PROPHYLAXIS
Stage 1 aims to recruit approximately 130 patients within 6 months. If progression rules are met, stage 2 will aim to recruit an additional 1091 patients within a further 30 months.

The expected average annual recruitment is 15-20 patients per site.

Progression criteria to the substantive phase

Go:

70-100% recruitment achieved. Progress to main trials following a review of screening logs and protocol. Any barriers for recruitment will be addressed.

Amend:

30-69% recruitment achieved. Potentially progress to main trial with additional sites being recruited as well as a screening log and protocol review, following discussion with Trial Steering Committee and HTA.

Stop:

Less than 30% recruitment achieved. The decision to progress will be made by the Trial Steering Committee in association with the HTA secretariat.

If the loss to follow-up (for those who have observed 6 months follow-up) exceeds 20%, without an identifiable and correctable reason it would not be feasible to progress to the substantive phase without substantial changes to the study design.

MAST-DURATION

Stage 1 aims to recruit approximately 50 patients within 12 months. If the progression rules are met, stage 2 will aim to recruit an additional 378 patients within a further 24 months. The expected average annual recruitment is 5-10 patients per site.

Progression criteria to the substantive phase

Go:

70-100% recruitment achieved. Progress to main trials following a review of screening logs and protocol. Any barriers for recruitment will be addressed.

Amend:

30-69% recruitment achieved. Potentially progress to main trial with additional sites being recruited as well as a screening log and protocol review, following discussion with Trial Steering Committee and HTA.

Stop:

Less than 30% recruitment achieved. The decision to progress will be made by the Trial Steering Committee in association with the HTA secretariat.

If the loss to follow-up (for those who have observed 6 months follow-up) exceeds 20%, without an identifiable and correctable reason it would not be feasible to progress to the substantive phase without substantial changes to the study design.

If either the DURATION or PROPHYLAXIS trial fails to recruit to target and subsequently doesn't proceed to stage 2, then recruitment to the other trial will continue under this protocol as appropriate.

8.4 Participants Trial Duration

MAST-PROPHYLAXIS

Trial duration will be approximately 24 months, consisting of a 7 day treatment period followed by a 14 day, 6 month, 12 month, 18 month and 24 month follow up.

MAST-DURATION

Trial duration will be approximately 24 months, consisting of either up to 3 months or at least 6 months treatment with a 6 month, 12 month, 18 month and 24 month follow up.

8.5 Trial Objectives

8.5.1 MAST-PROPHYLAXIS

Primary

To determine the comparative clinical effectiveness (absolute difference in the rate of PTS within the first 2 weeks post-TBI) of a 7-day course of phenytoin or levetiracetam, used as seizure prophylaxis, versus no AED for TBI patients.

Secondary

- Compare outcomes between the three arms
  - extended Glasgow Outcome Scale
  - cognitive function
  - quality of life (EQ-5D-5L)
    Liverpool Adverse Events Profile
- To compare adverse events between the three arms
- To compare the frequency of PTS between the three arms
- Compare the PTS rate between phenytoin and levetiracetam
- Undertake a detailed economic evaluation.

8.5.2 MAST-DURATION

Primary

To determine the comparative clinical effectiveness (absolute difference in the rate of late PTS within 24 months post-TBI) of a longer course of phenytoin or levetiracetam (at least 6 months) versus a shorter course (up to 3 months) for TBI patients with early seizures (within first 7 days following trauma).

Secondary

- Compare outcomes between the two arms
  - extended Glasgow Outcome Scale
  - cognitive function
  - quality of life (EQ-5D-5L)
  - Liverpool Adverse Events Profile
- To compare adverse events between the two arms
- To compare the frequency of PTS between the two arms
- Undertake a detailed economic evaluation.

Definition of a seizure

If a participant has a seizure they should contact their treating team. The participant should then be reviewed by a clinician to confirm whether a seizure has taken place. Participants will also be asked to report any seizures to the central coordination team. The GP will be sent a form asking them to confirm that a seizure has been clinically confirmed.

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

1. Simple partial seizures:

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

2. Complex partial seizures:

- with impairment of consciousness only
- with impairment of consciousness plus automatisms (lip smacking, fumbling, etc.)

3. Partial seizures with secondarily generalized seizures;

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

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

If performed as part of routine clinical care, electroencephalographic findings will be used as adjunct criteria in making a diagnosis of seizures.

During the period when participants are in-patients, it is anticipated that the occurrence of seizures will be confirmed by local clinical staff as per routine clinical practice. After discharge from hospital, participants and carers will be given a leaflets and have access to a video to allow them to recognise subtle manifestations of seizures.

8.6 Trial Outcome Measures

8.6.1 Primary outcome measure

MAST-PROPHYLAXIS: Occurrence of an acute symptomatic seizure within 2 weeks post-TBI.
MAST-DURATION: Occurrence of late PTS within 24 months post-TBI

8.6.2 Secondary outcome measures (both trials)

- Occurrence and time to PTS within 24 months post-TBI (MAST-PROPHYLAXIS ONLY)
- Extended Glasgow Outcome Scale, Neurobehavioral Symptom Inventory, quality of life (EQ-5D-5L), and Liverpool Adverse Events Profile at 6, 12, 18 and 24 months.
- Economic evaluation
- Frequency of PTS
- Mortality at 6, 12, 18 and 24 months.
- Adverse events of special interest during treatment.

9 Selection and withdrawal of participants

9.1 Inclusion Criteria

MAST-PROPHYLAXIS:

- Patients aged ≥10 years, with TBI managed in an NSU without an acute symptomatic seizure
- Patient or Legal Representative is willing and able to provide informed consent or in the absence of a legal representative, an Independent Healthcare Professional provides authorisation for patient randomisation within 48 hours of admittance.

MAST-DURATION:

- Patients aged ≥10 years with TBI managed in an NSU who have started on an phenytoin or levetiracetam due to an acute symptomatic seizure during acute hospitalisation
- Patient or Legal Representative is willing and able to provide informed consent or in the absence of a legal representative, an Independent Healthcare Professional provides authorisation for patient enrolment

9.2 Exclusion Criteria

MAST-PROPHYLAXIS:

The presence of any of the following will preclude patient inclusion:

- Post-traumatic seizures
- Unsurvivable injury
- Previous history of epilepsy
- Patients who are taking an AED pre-TBI
- Pregnancy or breastfeeding
- Any known hypersensitivity to study drugs (or hydantoins or pyrrolidone derivatives) or any of its excipients
- Time interval from the time of admission to NSU to randomisation exceeds 48 hours

MAST-DURATION:

The presence of any of the following will preclude patient inclusion:

- Unsurvivable injury
- Previous history of epilepsy
- Patients who are taking an AED pre-TBI
- Patient who has been clinically prescribed an AED to treat PTS (other than phenytoin or levetiracetam since current admission
- Any known hypersensitivity to study drug selected or any of its excipients
- For phenytoin: known hypersensitivity to other hydantoins
- For levetiracetam: known hypersensitivity to other pyrrolidone derivatives

9.3 Treatment Assignment

MAST-PROPHYLAXIS

Patients who fulfil the eligibility criteria will be randomly assigned to either phenytoin, levetiracetam or no AED for a period of 7 days. The distribution between trial populations will be 1:1:1 (phenytoin : levetiracetam : no AED).

MAST-DURATION

Patients who fulfil the eligibility criteria will be randomly assigned to a maximum of 3 months OR a minumum of 6 months duration of a clinically prescribed AED (phenytoin or levetiracetam, choice of drug at clinician's/site's local option). The distribution between trial populations will be 1:1 (<3 months:>6months). In the event of a seizure occurring within the trial period, treatment will continue as per local clinical guidelines regardless of the treatment arm. If treatment management changes within the trial period, patients will remain in the trial.

A secure electronic system will be used for the randomisation of suitable patients. Suitably trained staff will access the secure site and enter the patient details. 24-hour telephone support will be provided for randomisation and eligibility criteria by Trial Investigators or suitable trained delegated persons. Allocation will be stratified by depressed skull fracture (yes / no), intradural lesion (yes / no) and initial severity of injury (GCS 3-8, GCS 9-15).

9.4 Participant Withdrawal Criteria

Primary reasons for withdrawal may include:

- SUSAR
- Withdrawal from treatment - participants may voluntarily withdraw from treatment for any reason at any time, but continue to provide follow-up data
- Withdrawal from trial - participants may voluntarily withdraw from treatment for any reason at any time, and also withdraw from data collection
- Patients will be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason

Each patient has the right to discontinue their participation in the trial at any time. If an unconscious patient regains capacity and makes a request to be withdrawn from the trial, then this will be accepted. Incapacitated patients may also be withdrawn from the trial if the consultee requests withdrawal. In addition, the investigator may withdraw the patient from their allocated treatment arm if, subsequent to randomisation, a clinical reason for not providing the drug treatment is discovered.

Prophylaxis

If a participant stops taking the trial drug due to intolerance, they will not be able to cross over to the other arm. In this instance the participant will be treated clinically as necessary (i.e. receive another AED or no treatment as necessary) and will be withdrawn from trial treatment However, the participant will remain in the trial and continue to be followed, unless consent to continue data collection has been withdrawn.

Duration
If a participant stops taking the trial drug due to intolerance, they will be able to receive the other trial-permitted AED if the treating clinical team agrees. If the treating clinical team wishes to prescribe an AED other than levetiracetam or phenytoin, the participant will be withdrawn from trial treatment. However, the participant will remain in the trial and continue to be followed, unless consent to continue data collection has been withdrawn

As the trial is on an intention to treat basis, any data collected will remain in the trial and the patient will continue to be followed up unless consent to continue data collection has been withdrawn. Initially patients who have been withdrawn from the trial will not be replaced as the power calculation for the trial allows for a 12% loss to follow up, however the withdrawal rate will be monitored and patient replacement will be at the discretion of the Trial Steering Committee should it exceed 12%.

All discontinuations and withdrawals will be documented in the CRF. If a patient wishes to discontinue, anonymised data collected up until that point will be included in the analysis.

10 Trial Treatments

10.1 Treatment Summary

The IMPs in this trial are levetiracetam and phenytoin. This trial has been accepted as Type A against the competent authority risk-adaption criteria, i.e. 'no higher than the risk of standard medical care'

10.1.1 Levetiracetam

Levetiracetam is an anti-epileptic drug widely used in clinical practice both for the treatment and prevention of post-traumatic and epileptic seizures.

10.1.1.1 Legal status

Levetiracetam is licensed for the treatment of epileptic seizures in adults but not for prophylaxis. It is, however, widely used off-license for treatment and prevention of PTS as discussed throughout this protocol. Standard clinical dosing as per the BNF will be adhered to.

Levetiracetam is not licensed for the treatment of PTS in children under the age of 12, although is routinely given in practice. As monotherapy, levetiracetam is only licensed from 16 years old. As an adjunct treatment however, it is licensed from 1 month of age. For children up to the age of 17 it is prescribed per body weight, in 2 categories of 'up to 50kg' and 'above 50kg'. The dosing will adhere to the children's BNF dosing regimen

10.1.1.2 Supply

Any product with a UK marketing authorisation may be used within the study. The IMP is to be supplied from standard hospital stock during in-patient stay and discharge prescription as appropriate. Post-discharge supplies may be supplied via primary or secondary supply routes (e.g. GP prescription supplied via community pharmacy). Any prescription charges incurred by patients or postage charges incurred by sites will be reimbursed by the trial. No trial specific labelling is required.

10.1.1.3 Storage conditions

Storage will be as detailed in the SmPC for specific brands and formulations in use at participating site.

10.1.1.4 . Maximum duration of treatment of a participant

MAST-PROPHYLAXIS: Participants will receive a course of 7 days of either phenytoin or levetiracetam or no drug.

MAST-DURATION: Participants will receive a maximum of up to 3 months or a minimum of 6 months as determined by the randomisation. The maximum possible duration of treatment during the trial is 24 months dependent on clinical need

10.1.1.5 Dose

1. Prescribing should be in line with the BNF recommendations and local prescribing practices. The prescription for individual patients will be left to the discretion of the prescribing clinician at the time, which should be in line with the BNF guidance but we are aware differing clinical scenarios will arise meaning individual doses may vary. Additional guidance can be found in the MAST Trial Procedures Manual.

2. If patients are experiencing recurrent seizures then the withdrawal regime should not be started and that patient should continue with their prescribed medication, as per clinical practice.

10.1.1.6 Administration

Levetiracetam can be administered orally, intravenously or via an enteral feeding tube

10.1.1.7 Known drug reactions

Drug reactions are as detailed in the SmPC.

10.1.2 Phenytoin

Phenytoin is an AED widely used in clinical practice both for the treatment and prevention of seizures.

10.1.2.1 Legal status

Phenytoin is licensed for use in the UK both to prevent and to treat post traumatic seizures following severe head injury.

10.1.2.2 Supply

Any product with a UK marketing authorisation may be used within the study. Both phenytoin and phenytoin sodium products are permitted. The IMP is to be supplied from standard hospital stock during in-patient stay and discharge prescription as appropriate. Post-discharge supplies may be supplied via primary or secondary supply routes (e.g. GP prescription supplied via community pharmacy).Any prescription charges incurred by patients or postage charges incurred by sites will be reimbursed by the trial. No trial specific labelling is required.

10.1.2.3 Storage conditions

Storage will be as detailed in the SmPC for specific brands and formulations in use at participating site.

10.1.2.4 Maximum duration of treatment of a participant

MAST-PROPHYLAXIS: Participants will receive a course of 7 days of either phenytoin or levetiracetam or no drug.

MAST-DURATION: Participants will receive a maximum of up to 3 months or a minimum of 6 months as determined by the randomisation. The maximum possible duration of treatment during the trial is 24 months dependent on clinical need.

10.1.2.5 Dose

1. Prescribing should be in line with the BNF recommendations and local prescribing processes. The prescription for individual patients will be left to the discretion of the prescribing clinician at the time, which should be in line with the BNF guidance but we are aware differing clinical scenarios will arise meaning individual doses may vary. Additional guidance can be found in the MAST Trial Procedures Manual.

2. If patients are experiencing recurrent seizures then the withdrawal regime should not be started and that patient should continue with their prescribed medication, as per clinical practice.

10.1.2.6 Administration

Phenytoin can be administered orally, intravenously or via a nasogastric tube.

10.1.2.7 Known drug reactions

Drug reactions are as detailed in the SmPC.

10.2 Concomitant Therapy

Any concomitant therapy clinically required will be permitted. Contraindications are listed in section 4.3 of the relevant SmPCs. A list of drug interactions is detailed in section 4.5 of the relevant SmPCs for both drugs. Any concomitant therapies which interact with the trial drugs will be recorded. Potential drug interactions with concomitant medications should be managed as per standard clinical practice, including therapeutic drug monitoring as appropriate. Accountability and dispensing

10.3 Accountability and dispensing

10.3.1 Pharmacy responsibilities

IMPs will be provided directly using standard hospital stock during inpatient stay (including use of ward stock where appropriate) with no requirement for trial specific dispensing.

10.3.2 Drug accountability

Drug accountability is not required as the drugs will be administered in line with routine standard care practices. Compliance will be measured using inpatient records and post-discharge at 6 month follow-up.

11 Procedures and assessments

11.1 Participant identification

All patients who have been admitted to the Neurosurgical Unit (NSU) with a traumatic brain injury will be screened for eligibility for both trials based on their clinical presentation. A member of the clinical team will assess potential eligibility of these patients based on the inclusion/exclusion criteria outlined in Section 9.1 and 9.2.

11.2 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each participant signed informed consent form.

Should a participant or participants legal representative require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators. A locally translated PIS will also be provided if required.

Consent must be taken prior to study randomisation.

Where potential patients fulfil the eligibility criteria, they will be approached by a member of the research team who will provide the patient information sheet and clarify any information from the patient which may preclude recruitment. Wherever possible informed consent will be obtained from the patient, however, due to the nature of the condition, this may not be possible.

Patient legal representative available in the hospital
In patients lacking capacity, a legal representative will be sought. If the legal representative is available in the hospital, is contactable, or is due to visit the patient within a reasonable timescale, then they will be provided with information about the trial and asked if they will provide consent for the patient before enrolment. This will take place during their visit to the patient.

For the purposes of sites in England, Wales and Northern Ireland, a legal representative is defined as:

A person not connected with the conduct of the trial who is:

(a) Suitable to act as the legal representative by virtue of their relationship with the adult, and
(b) Available and willing to do so.

For the purposes of sites in Scotland, a legal representative is defined as:

(a) Any guardian or welfare attorney who has power to consent to the adult's participation in research.
(b) If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.

Patient legal representative not available in the hospital
Due to the condition of these patients, there will be those who will have no registered legal representative or where the legal representative is not contactable or able to visit the hospital at short-enough notice to be able to enrol the patient in a timely manner. In such cases we advocate enrolment would be possible with written agreement from an independent clinician. Starting the study drug as soon as possible after admission to the NSU is perceived to gain maximum effect of a 7 day course of an AED. If no legal representative is available for discussion then an independent clinician will be approached. If a legal representative visits the hospital at a later date then the trial will be discussed with them and their consent sought at that time point to continue in the trial.

Patients who regain capacity whilst in hospital will be informed about the clinical trial and consent to continue will be sought. If at any stage either the legal representative or the patient chose to withhold consent then the patient will be withdrawn from the trial.

Patients who regain capacity following discharge will be contacted by phone and posted a patient information sheet and consent from as soon as possible.

Independent healthcare professional (IHP) definition
For the purposes of the MAST trial, the Independent Healthcare Professional (IHP) is defined as:

A person who is not connected with the conduct of the trial, specifically:
a) The sponsor of the trial;
b) A person who undertakes activities connected with the management of the trial;
c) An investigator of the trial or;
d) A health care professional who is a member of the investigators delegated team for the purposes of the trial.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible, verbally if the participant is in hospital, by post if they have been discharged.

The Medicines for Human Use (Clinical Trials) Regulations prohibit children under the age of 16 from giving consent to take part in CTIMP. Therefore consent will be sought on behalf of children from parents or a legal representative. Whenever practical and appropriate, the child's assent will be sought.

A flowchart depicting the consent process is illustrated in Figure 2.

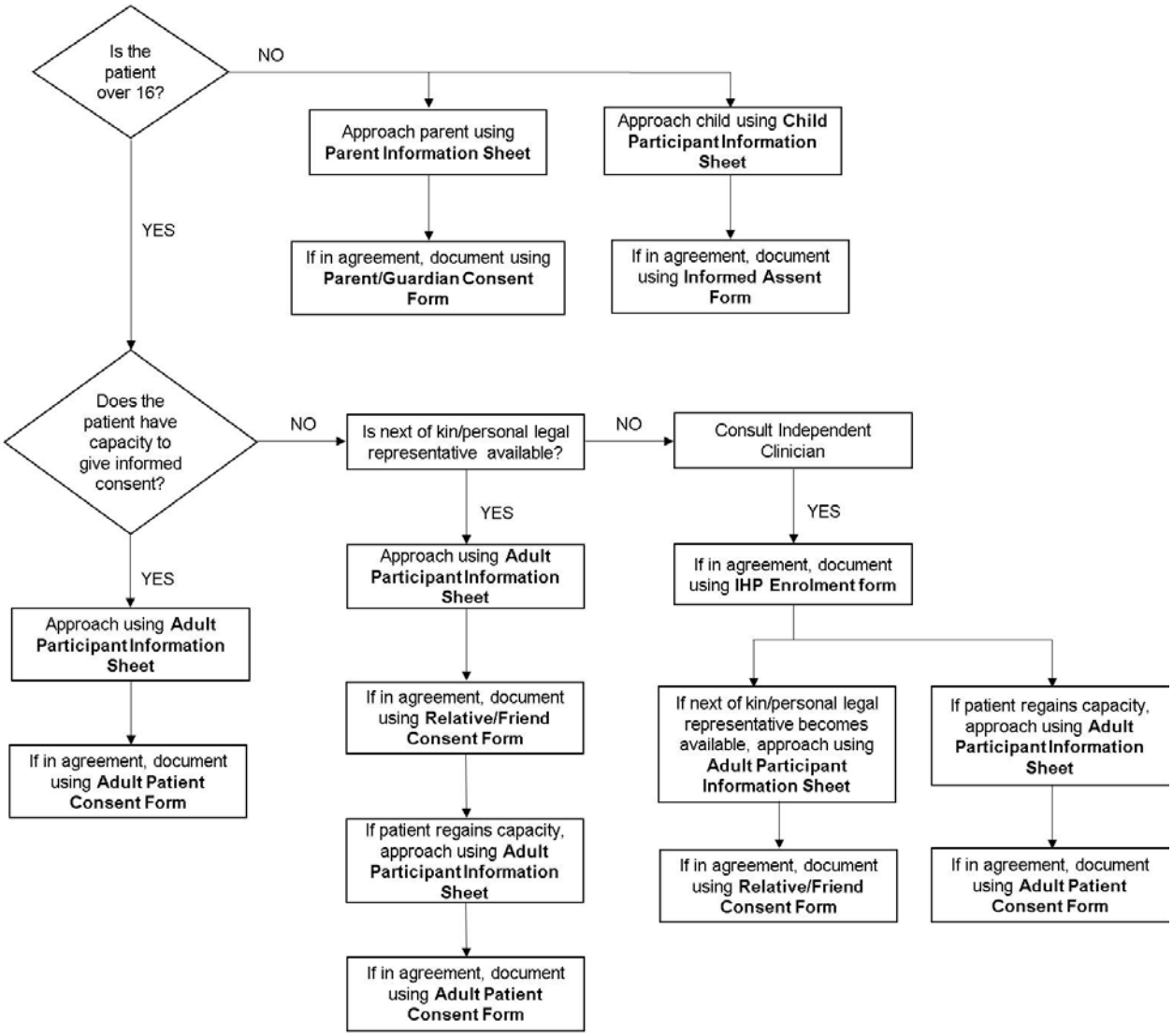


Figure 2: Flowchart of the consent process

11.3 Screening evaluation

11.3.1 Screening Assessments

Trial specific assessments will only be conducted after participants have given written informed consent. Medical history which would preclude eligibility will be obtained from either the patient case notes or after discussion with the patient (or patient's representative – if available).

11.3.2 Participant Registration/Randomisation

Upon completion of consent and screening, patients are enrolled to either MAST-DURATION or MAST-PROPHYLAXIS based on their clinical presentation. A unique participant ID will be allocated to each patient. The initial section of the CRF will then be completed.

All patients enrolled into MAST-DURATION will be provided with a study wristband, to be applied before their first dose of medication and worn whilst they are an inpatient. This highlights that they are taking part in a research study and are receiving either phenytoin or levetiracetam. This is to help ensure the nursing staff at onward community hospitals or rehabilitation units are aware of the study at all times, and to ensure continuity of prescribed treatment. Wording on the wrist bands will read 'MAST TRIAL. PLEASE GIVE DRUG AS PRESCRIBED'.

All patients enrolled into MAST-DURATION will also be provided with a participant ID card. This is in case they need to show it to anyone who gives them medical attention and contains the name of the trial, whether they are receiving phenytoin or levetiracetam, the duration of the treatment and contact details for the local research site team and sponsor.

Patients enrolled in MAST-PROPHYLAXIS will not require a participant ID card or wristband as they are unlikely to leave hospital before the 7 days of treatment is complete.

Following randomisation, a letter will be sent to the patient's GP for both trials, informing the GP about the patient's participation, including which drug they are receiving, the duration of treatment and follow-up assessments. GPs will be advised that any further prescribing requirements will be forwarded in the discharge summary, as per routine clinical practice.

An anonymised record of the patients approached along with the numbers of, and reasons for, screen failures and refusal of consent will be kept at each site on a screening log and reported to the Trial Co-ordinating Centre on a monthly basis. This information will be used to identify any barriers to recruitment and allow improvement measures to be identified and implemented in a timely manner.

11.4 Screening & Baseline Assessments

All patients will have a medical history taken and a clinical examination as part of the routine standard care. The following are to be recorded in part 1 of the case report form (CRF):

- Inclusion/exclusion criteria review
- Informed consent process followed and consent or authorisation for enrolment
- Obtained
- Urine pregnancy test (if applicable) for females of child bearing potential
- Routine review of clinical laboratory results
- ECG (if indicated by local policy)
- Standard of Care:
    - Patient medical history (including co-morbidities and relevant medications)
    - Patient demography
    - Injury related events - date of TBI, date of PTS, date of possible intubation, date of AED
    - Neurological status
    - Imaging review

11.5 Trial assessments

11.5.1 Timing of assessments

Patients will be monitored as per routine clinical practice in the Neurosurgical Unit until discharge and thereafter at 6 months, 12 months, 18 months and 24 months (+/- 8 weeks at each time point) in both studies to score clinical outcome. Patients in the MAST-PROPHYLAXIS study will also be followed up at 14 days. Patients from the MAST-PROPHYLAXIS study may also be followed up at 60 months, subject to additional funding (+/- 8 weeks).

11.5.2 Assessments at time point

- Adverse events of special interest review during treatment.
- Assessment for seizures during hospital admission, at discharge at day 14 (by telephone if patient is already discharged) (PROPHYLAXIS only)
- EQ-5D-5L questionnaire at discharge

- Follow up postal questionnaire/email/telephone call at 6 months (+/- 8 weeks), 12 months (+/- 8 weeks), 18 months (+/- 8 weeks), 24 months (+/- 8 weeks) post randomisation
  To document:
  - Occurrence of seizures
  - GOSE questionnaire
  - NSI questionnaire
  - EQ-5D-5L questionnaire
  - Liverpool Adverse Events Profile questionnaire

11.5.3 Assessments at the end of trial visit

At the end of the trial a health economic evaluation will be performed.

11.6 Schedule of Assessments

MAST-PROPHYLAXIS

Assessment	Screening/ baseline	Treatment phase end	Follow up			Follow up visits	End of Study
Visit	1	2	3	4	5	6	7
	Day 1	Day 7	Day 14	6 mths	12 mths	18 mths	24 mths
Eligibility assessments	x						
Informed consent	x						
Urine pregnancy test (if applicable)	x						
Randomisation	x						
ECG (if indicated by local policy)	x						
CRF Part 1	x						
IMP administration	x	x					
AESI assessments and CRF completion	x	x					
Concomitant medications	x	x					
Occurrence of seizures		x	x	x	x	x	x
GOS questionnaire				x	x	x	x
NSI questionnaire				x	x	x	x
EQ-5D-5L questionnaire			x	x	x	x	x
Liverpool Adverse Events Profile questionnaire				x	x	x	x
Economic evaluation							x

MAST-DURATION

Assessment	Screening/ baseline		Treatment phase			Follow up visits	End of Study
Visit	1	2	3	4	5	6	7
	Day- 1	discharge	3 mths	6 mths	12 mths	18 mths	24 mths
Eligibility assessments	x						
Informed consent	x						
Randomisation	x						
CRF stage 1		x					
Treatment duration<3mths	x	x	x				
Treatment duration>6mths	x	x	x	x	x*	x*	x*
AESI assessment	x	x		x			
Concomitant medications	x	x					
Occurrence of seizures	x	x		x	x	x	x
GOS questionnaire				x	x	x	x
NSI questionnaire				x	x	x	x
EQ-5D-5L questionnaire		x		x	x	x	x
Liverpool Adverse Events Profile questionnaire				x	x	x	x
Compliance check				x			
Economic evaluation							x

* If clinical indicated

11.7 Long-Term Follow-up Assessments

Participants will be followed up for 24 months post randomisation by postal questionnaire. However, if after approximately 2 weeks the questionnaire has not been returned then patients will be followed up by telephone. If the time point after an assessment exceeds 8 weeks, and there is no response, then the patient will be deemed as lost to that follow up. Where patients attend for a routine clinical follow-up they will be reviewed.

11.8 End of Trial Participation

Participants will continue normal standard of care following their participation in the trial.

11.9 Trial restrictions

There are no trial related restrictions in addition to standard care.

The management of any post-traumatic seizures will be based on the clinical assessment of the participant. Regardless of the trial arm the participant is assigned to, and the trial medications being/not being taken, the treating clinician will assess the participant regularly and will decide whether additional treatment is indicated. This may include additional anti-epileptic medication.

Trial medicines could reduce the effectiveness of oral contraceptives. It is therefore necessary to advise all participants, to take extra precautions while taking the trial medication and consider using alternative forms of contraception. If it becomes evident that a child between 10 and 16 years is sexually active, then safeguarding concerns will be discussed with the local site's named or designated safeguarding professional. Contraceptive advice is a particularly sensitive issue for young people and the Child PIS advises that their doctor will be able to discuss alternative types of contraception with them confidentially. Paediatric Certified Nurse Practitioners will be able to discuss this with them if they prefer. They will also be advised that their parents/legal guardians can provide more details on which types of contraception are suitable for them in this study.

Contraception advice will be as clinically directed. Due to the risks associated with Phenytoin, women of childbearing potential who are taking this IMP, who are in MAST-DURATION, will be advised not to become pregnant during treatment, or within one month of stopping IMP.

12 Assessment of Safety

Phenytoin is licensed for the treatment of epileptic seizures and for the prevention and treatment of PTS. Levetiracetam is licensed as monotherapy for the treatment of epileptic seizures in adults >16 years old, and as an adjunct treatment from 1 month of age. Levetiracetam is not licensed for either the treatment or prevention of PTS. It is, however, widely used off-license in both indications, in both adults and children. In a survey conducted at all UK neurosurgical units it was found that levetiracetam is more frequently prescribed than phenytoin for seizure prophylaxis [11].

The safety profiles of both drugs are well established and the trial participants will be assessed at regular intervals throughout the trial, over and above routine clinical care. Given the pragmatic nature of the trial, and that the potential risk associated with the study drug is 'no higher than standard care', the MAST trial will utilize the following risk-adapted safety reporting approach:

SAEs will be recorded in the CRF but not reported to the sponsor unless they are deemed to be SARs or SUSARs.

- Reactions that are either serious (SARs) or serious and unexpected (SUSARs) will require expedited reporting. Principal Investigators will be required to record and report SARs and SUSARs to the Sponsor as described in section 12.5

- All SAEs will be captured on the CRF for review by the CI (or delegated member of the coordination team).

- The resulting report listing of SAEs will be reviewed by the CI and reported to the Sponsor every 6 months.

- Reports of SAEs and reported SARs & SUSARs will form the basis of the Development Safety Update Report (DSUR) to be submitted annually to the MHRA and REC.

Principal investigators are not required to report to the central coordinating team any AEs or ARs unless these fulfill the criteria for a SAR or SUSAR.

12.1 Definitions

12.1.1 Adverse event (AE)

Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Please note: Recording of adverse events must start from the point of Informed Consent regardless of whether a participant has yet received a medicinal product.

However due to the pathology of traumatic brain injury, where the patients will be regularly monitored in the intensive care environment or on the neurosurgical wards, it is not practicable to record all adverse events. Therefore only adverse events of special interest (AESIs) will be recorded and **reportable** serious adverse events (SAEs) will be reported in accordance with this protocol. (Please see Section 12.1.4 for details of SAEs that are exempt from expedited reporting.)

Adverse events of special interest (AESI)
The following should all be recorded on the AESI form in the CRF for both trials:

Phenytoin arm

- Cardiovascular: Cardiac arrhythmia, circulatory shock;
- Central nervous system: phenytoin toxicity - (nystagmus +/- unsteady gait +/- slurred speech +/- confusion). Drowsiness, suicidal ideation/tendencies;
- Dermatologic: Bullous dermatitis, skin rash;
- Gastrointestinal: Gingival hyperplasia;
- Genitourinary: Peyronie's disease;
- Hematologic: Macrocytosis, megaloblastic anaemia;
- Hepatic: Dupuytren's contracture, hepatitis ;
- Injection site reaction: Purple glove syndrome: oedema, discolouration and pain distal to injection site.

Levetiracetam arm

- Central nervous system: Behavioural problems including: aggression, agitation, anger, anxiety, apathy, depersonalisation, emotional lability, irritability, neurosis, psychotic symptoms, suicidal ideation/tendencies.

12.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

12.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI)

When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant /event outcome or action criteria.

12.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires re-hospitalization or prolongation of existing inpatients´ hospitalization, where it is not considered to be due to the initial trauma.
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect.

- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

12.1.6 Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

The RSI is contained in a clearly identified section of the Summary of Product Characteristics (SmPC)

For this trial the Reference Safety Information is: section 4.8 – Undesirable effects, of the Flynn Pharma Ltd, Phenytoin Sodium Flynn Hard Capsules 300mg SmPC and the Zentiva Levetiracetam 750mg Film-Coated Tablets SmPC. The applicable SmPC version will be the latest version that has been approved by the MHRA for use in this trial.

12.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 12.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 12.5

12.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

Expected SAEs exempt from expedited reporting
Due to the nature of traumatic brain injury, affected individuals can often develop surgical and medical complications. Expected systemic or surgical complications associated with TBI will not be reported as SAEs However, all SAEs (both reportable or non-reportable) will be captured on the study CRF (Case Report Form) or SAE recording log in the Investigator Site File, so that all serious adverse event data is captured.

In addition, any of the following systemic SAEs are also exempt from expedited reporting:

Pulmonary

- Pneumonia
- Pneumothorax
- Atelectasis
- Aspiration
- Pleural effusion/empyema
- Ventilator-related complications
- Adult respiratory distress syndrome
- Need for prolonged mechanical or positive pressure airway ventilation

Cardiac

- Angina
- Pericardial effusion
- Pericarditis

Renal

- Urinary tract infection
- Urinary retention
- Haematuria
- Renal dysfunction
- Renal failure maybe requiring full renal support

Thrombotic

- Deep vein thrombosis
- Pulmonary embolism
- Mesenteric thrombosis
- Other thromboses (e.g. limb)

Hepatobiliary

- Pancreatitis
- Liver failure

Bowel

- Infective diarrhoea or colitis (e.g. Clostridium difficile)
- Diarrhoea of other causes
- Bowel ischaemia
- Ileus

Wound other than craniotomy or craniectomy

- Infection
- Dehiscence

Other miscellaneous general complications

- Decubitus ulcer
- Other infections (e.g. MRSA)
- Anaesthetic-related complication
- Coagulopathy
- Pyrexia
- Septicaemia

12.4 Evaluation of adverse events

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality).

12.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4.This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

12.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probably: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probably and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

12.4.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

12.4.4 Recording of adverse events

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the CRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 12.5.

12.5 Reporting Serious Adverse Events

Each Principal Investigator needs to record all adverse events of special interest and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all reportable SAEs to the Sponsor immediately but not more than 24 hours of first notification. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all reportable serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

The completed SAE form can be emailed. Details of where to report the SAEs can be found on the MAST SAE form and the front cover of the protocol.

12.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 12.1.6 for the Reference Safety Information to be used in this trial.

12.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- competent authorities in the concerned member states (eg MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

12.6.2 When to report?

12.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 12.5.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

12.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 12.5.1 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

12.6.3 How to report?

12.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product
b) an identifiable participant (e.g. trial participant code number)
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source

and, when available and applicable:

- an unique clinical trial identification (EudraCT number or in case of non- European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number)

12.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

12.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

12.7 Pregnancy Reporting

All pregnancies reported in trial participants during the treatment phase of the trial and for 1 month post treatment should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/fetus. If the outcome meets the serious criteria, this would be considered an SAE.

13 Toxicity – Emergency Procedures

In the event of suspected occurrences of major toxicity, the trial drug will be withdrawn.

14 Evaluation of Results (Definitions and response/evaluation of outcome measures)

All data will be presented to the Data Monitoring Committee, who will meet on a regular basis throughout the trial. The DMC will then prepare a report for the Trial Steering Committee who will provide overall supervision of the trial.

14.1 Response criteria

14.1.1 Mortality

This will be measured from the date of randomisation to the 24 month follow up and will be reported for all deaths due to all causes. The cause of death is to be recorded if known.

14.1.2 Quality of life

Quality of life will be assessed by means of the EQ-5D-5L questionnaire to generate quality adjusted life years.

14.1.3 PTS recurrence

PTS recurrence will be measured from the date of randomisation to the 24 month follow up and will be reported for all causes.

15 Storage and Analysis of Samples

Urine pregnancy test samples will be analysed at point of care and then discarded. These will be the same point of care tests used during normal clinical practice. No further samples will be collected or stored as part of this trial.

16 Statistics

16.1 Statistical methods

The main statistical analysis will be performed on an intention-to-treat basis, which will include all randomly assigned participants.

The primary endpoint (occurrence of PTS) is binary (yes / no). The primary analysis will estimate the absolute difference between the active treatment groups and control in terms of the incidence of PTS using logistic regression with an additive link, adjusting for baseline covariates (subdural haematoma (yes / no), number of lobes with a contusion (none / one / two / more than two), craniotomy or craniectomy (yes / no), depressed skull fracture (yes / no), initial severity of injury GCS 3-8 / 9-15, intradural lesion (yes / no) and will furnish the estimates with 95% confidence intervals. MAST DURATION will use a standard 2-sided p-value compared to a 5% significance level; MAST-PROPHYLAXIS will adjust for multiple testing using Dunnett's test at an overall 5% significance level stipulating that the smaller of the 2-sided p-values must be less than 2.7% to achieve statistical significance. A direct comparison between active arms (phenytoin vs levetiracetam) in MAST-PROPHYLAXIS will be a secondary analysis. The baseline covariates will be those used to stratify the randomisation: depressed skull fracture (yes / no), intradural lesion (yes / no) and initial severity of injury (GCS 3-8, GCS 9-15). Site will be handled as a random effect as there are anticipated to be 29 sites.

Sensitivity analyses will be performed to assess the influence of missing data and deviations from the intention-to-treat principle.

The GOSE will be analysed with an ordinal method adjusting for baseline covariates. Further secondary endpoints will be summarized using appropriate techniques according to whether the variable is binary, categorical, continuous or time-to-event. Categorical and binary variables will be summarized using bar charts, frequency tables and comparisons made using logistic regression.

Continuous variables will be summarized, broken down by treatment arm, using Box plots, mean, median, SD, max, min and compared using linear regression. Time-to-event variables will be summarized using Kaplan-Meier plots, and compared using the log-rank test. Pre-defined subgroups for exploratory analyses will be: subdural haematoma (yes / no), number of lobes with a contusion (none / one / two / more than two), craniotomy or craniectomy (yes / no), depressed skull fracture (yes / no), initial severity of injury GCS 3-8 / 9-15, intradural lesion16.1 (yes / no), lesion site (temporal, insular, frontal, parietal, occipital, basal ganglia, thalamo-capsular, posterior fossa) and lesion type (extradural hematoma, acute subdural haematoma, contusion, chronic subdural haematoma, diffuse axonal injury, skull vault fracture, other). A detailed statistical analysis plan will be prepared by the study statistician without reference to the unblinded data.

16.2 Interim analyses

The primary purpose of the pilot is to assess recruitment rates rather than to make sample size adjustments, see section 8.3 for further details.

An interim analysis (blinded to all except the IDMC: Independent Data Monitoring Committee) may be performed after an appropriate number of patients have observed 14 days follow up for Prophylaxis and 24-month follow-up for DURATION, shortly before recruitment is scheduled to be halted, in order to confirm the sample size. The TSC, IDMC and statistical team will agree jointly on the most appropriate timing of this interim analysis, taking into account the case mix and parameters the IDMC wishes to estimate. If the sample size needs to be revised, we are able to incorporate the uncertainly in absolute seizurerates of 11% for MAST-PROPHYLAXIS and 25% for MAST-DURATIONin order to achieve an acceptable conditional power as

determined by the IDMC.

The interim analysis will be outlined in the IDMC Charter.

16.3 Number of Participants to be enrolled

A 12% drop-out rate is assumed in both trials.

MAST-PROPHYLAXIS

According to the available evidence (5,6), a treatment effect of 7% can be expected with seizure prophylaxis. We will attempt to reproduce these findings in a multi-centre setting across the NHS. Recruiting 1221 patients overall will provide 358 observations per arm. Assuming seizure rates of 4% in both active arms and 11% in control will provide 90% power to achieve significance in both comparisons. Alternatively, if only one active arm has a seizure rate of 4% and the other the same rate as control, then there will be 91% power to achieve significance in that individual comparison. The expected average annual recruitment is 15-20 patients / site. We will aim to roll out the trial in 29 adult trauma-receiving hospitals in the UK. According to the timeline presented below, the recruitment will be completed in 3 years.

MAST DURATION

A course of phenytoin or levetiracetam (up to 3 months) for patients with PTS in the acute phase. Hence, we are starting from the premise that the shorter AED duration is 'standard' practice. The longer AED duration course will potentially decrease the PTS rate. Therefore, the proposed study will be a superiority trial. In view of the potential for increase in side effects with a longer course, we will aim for a relatively large treatment effect of 13% (NNT 7.7), as this is felt necessary in order to lead to a change in clinical practice in the 'real -world'.

Recruiting 428 patients overall will provide 188 observations per arm. Assuming seizure rates of 12% and 25% in the intervention and control arm will provide 90% power. The expected average annual recruitment is 5-10 patients / site. We will aim to roll out the trial in 29 adult trauma-receiving hospitals in the UK. According to the timeline presented below, the recruitment will be completed in 3 years.

16.4 Criteria for the premature termination of the trial

There are no defined criteria for the premature discontinuation of the trial. However the DMC and TSC will make recommendations on the discontinuation of the trial following review of the ongoing data presented at regular scheduled meetings.

16.5 Procedure to account for missing or spurious data

For the primary analysis missing data will be assumed to be missing at random. A sensitivity analysis will be carried out by performing a complete case analysis. As the relevant covariates need to be recorded before the patient can be randomised, we aim to have minimal missing baseline data. There is also an excellent track record for UK-led neurosurgical studies in achieving extremely high rates for follow-up (STICH, STICH II and RESCUEicp studies).

16.6 Economic evaluation

An economic analysis will be conducted alongside both trials. The following common methods will be used in both studies. Costs will be based on an NHS perspective and a standard price year, and include details of all AED treatment and hospital admissions (we propose to extract the latter from the NHS Digital Hospital Episode Statistics (HES) database). Resources associated with AED treatment will thereby be monitored along with original length of stay and any hospital re-admissions.

In terms of outcomes, data on quality of life, measured using the EQ-5D-5L [18], will be requested at neuroscience unit (NSU) discharge, 6, 12, 18 and 24 months post-enrolment (if

the participant cannot complete the EQ-5D-5L themselves, we will request that a relative/friend complete the proxy version). This will enable Quality Adjusted Life Year (QALY) scores to be estimated using the total area under the curve method [19], taking account of the latest appropriate guidance [20].

The within trial analysis will be conducted on an intention to treat basis over a 24-month period, with appropriate discounting [21]. Assuming the level of missing data is not large i.e. <20% a complete case analysis will be undertaken. Alternatively, multiple imputation will be undertaken, where patterns of missing data would be examined to infer the assumed missing data mechanism [22]. Regression analysis will be used to estimate the incremental cost and incremental effect (QALY gain) associated with both a longer course of AED (phenytoin or levetiracetam) compared to a shorter course of AED (MAST-DURATION) and a 7-day course of AED (phenytoin or levetiracetam) compared to no AED (MAST-PROPHYLAXIS).

Assuming dominance does not occur (this would be apparent if one intervention was both more costly and less effective), the incremental cost-effectiveness ratio (ICER) will be estimated (mean incremental cost/mean incremental effect) by comparing the remaining interventions in both studies. These ICERs will then be compared to thresholds of cost-effectiveness [21] in order to consider the potential value for money/make recommendations about provision in the NHS. Additionally, the associated level of uncertainty will also be estimated, where the cost-effectiveness acceptability curve (CEAC) will be calculated. The CEAC estimates the probability of the intervention being cost-effective at various levels of willingness to pay [23].

Finally, sensitivity analysis [24] will be undertaken on the above base-case analysis to assess whether the associated conclusions are robust to changes in key assumptions. Potential sensitivity analysis would include an assessment of whether results are robust to different assumptions about missing data and could be based on a complete case approach if MI were used in the base-case, or MI could be undertaken if a complete case approach was undertaken in the base-case. Another sensitivity analysis might be to adopt as per protocol approach and exclude any individuals who did not receive the treatment to which they were assigned.

16.7 Definition of the end of the trial

The end of the main trial will be the date of the last patient's final assessment/loss to follow-up.

17 Data handling and record keeping

17.1 eCRF

Electronic case report forms will be used to collect the data. All data will be entered onto a secure electronic database. The database, which will be MHRA and GDPR compliant, will be secured by appropriate access control and password protection. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Data provided to the central coordinating team will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the central coordinating team will request that the data be clarified.

Study participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the study. The MAST trial management team will hold identifiable data on all

participants including name, date of birth, gender, NHS number or equivalent, home address and postcode, telephone number and email address where applicable.

Patient identifiable data (PID) will be accessible to limited members of the MAST trial team within the Cambridge Clinical Trials Unit, sponsor monitors auditors and inspectors as required. It is necessary to 1) perform linkage to national datasets (NHS Digital, Secure Anonymised Information Linkage, Public Health Wales, electronic Data Research and Innovation Service, Public Health Scotland and Belfast Health and Social Care Trust, and 2) to contact participants for follow-up assessments and is therefore imperative to the conduct of the study.

All PID downloaded from NHS Digital and the equivalent national health record organisations will be stored securely on the University of Cambridge, School of Clinical Medicine Secure Data Hosting Service (SDHS). The SDHS is registered and approved under the NHS Digital Data Security and Protection Toolkit and is ISO 27001 certified.

17.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., hospital records) and all original signed informed consent forms. The electronic CRFs should also be readily available.

In this trial the following documentation will be considered as source data:

- Patient medical notes, electronic and/or paper as applicable
- Screening Logs
- Informed Consent Forms
- Questionnaires
- GP seizure confirmation form
- Source data worksheets will be provided to sites to us as required to assist them in documenting medical history, concomitant medications, and adverse events and adverse reactions.

17.3 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of GDPR, the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

18 Data Monitoring Committee/Trial Steering Committee

The TSC will provide overall supervision with respect to the conduct of the trial. The independent chair of the TC will be Professor Anthony Bell. Full details of the TSC membership and remit can be found in the TSC charter.

The ethical and safety aspects of the trial will be overseen by an independent DMC which will be chaired by Professor Martin Smith. IDMC meetings will be timed so that reports can be fed into the TSC meetings. Full details of the IDMC membership and remit can be found in the IDMC Charter.

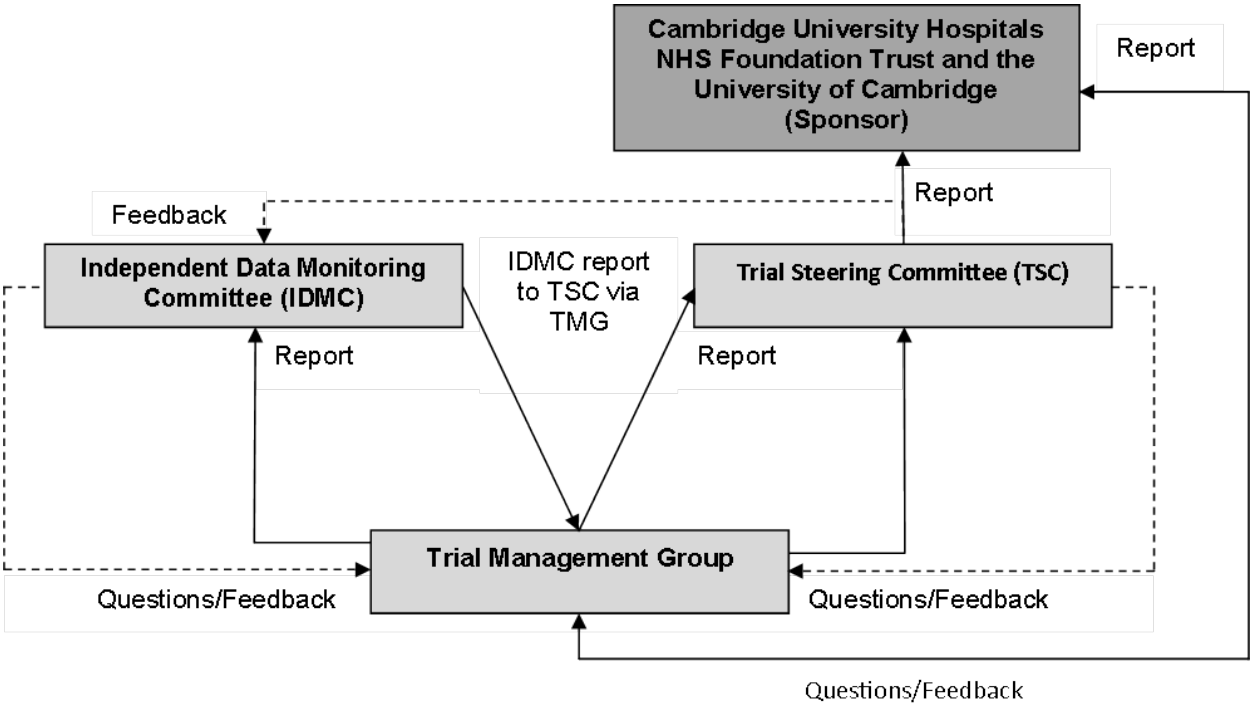


Figure 3: Diagram of Relationships between Trial Committees and Group

19 Ethical & Regulatory considerations

Health Research Authority review for all UK sites

19.1 Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

19.2 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

19.3 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

19.4 Peer Review

The trial proposal has been through the NIHR peer review process as a requirement of the HTA award. It has also been discussed and widely accepted by the Academic Committee of the Society of British Neurological Surgeons, the Age and Ageing National Specialty Group of the NIHR CCRN and the British Neurosurgical Trainee Research Collaborative. The support of the UK Neurosurgical Research Network will allow us to roll-out the substantive trial across the NHS.

19.5 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

19.6 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

20 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

This study is funded by the National Institute for Health Research (NIHR) HTA Programme Grant (NIHR128226). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

21 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

22 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Regarding missed study medication, only deviations deemed to be either clinically significant or where the trial site staff caused the error/deviation will be documented as protocol non-compliance. Where patients refused or missed trial medication at their own volition, this will be documented but not reported as protocol non-compliance.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

23 Publications policy

Ownership of the data arising from this trial resides with the coordinating trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report (FSR) will be prepared.

The findings of the MAST trial will be disseminated via peer-reviewed journals and presentations at national and international meetings. In addition to meetings orientated around neurosurgery, conferences organised for the different health professionals who care for patients post traumatic brain injury will be targeted.

Research findings will be disseminated to relevant service user groups and charities (eg Headway) through newsletters, website posts and public presentations. The MAST trial website will also include dedicated pages for members of the public. The trial will be presented in open days organised by hospitals participating in the trial where members of the public are invited to find out about ongoing research. Talks/presentations will also be given at meetings of local/regional relevant service user groups and charities (Headway local branches).

24 References

1. Menon DK, Schwab K, Wright DW, Maas AI, The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position Statement: Definition of Traumatic Brain Injury. YAPMR. Elsevier Inc; 2010 Nov 1;91(11):1637–40.

2. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. The Lancet Neurology. Elsevier; 2008 Aug;7(8):728–41.

3. Lawrence T, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson PJ. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. BMJ Open. 2016 Nov 24;6(11):e012197–8.

4. Ritter AC, Wagner AK, Szaflarski JP, Brooks MM, Zafonte RD, Pugh MJV, et al. Prognostic models for predicting posttraumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury. Epilepsia. 2016 Jul 19;57(9):1503–14.

5. Temkin N, Dikmen SS, Alan J Wilensky, Keihm J, Chabal S, Winn R. A Randomized, Double-Blind Study of Phenytoin For The Prevention of Post-Traumatic Seizures. The New England Journal of Medicine. 1990 Aug 23;323(8):497–502.

6. De Smedt T, Raedt R, Vonck K, Boon P. Levetiracetam: the profile of a novel anticonvulsant drug-part I: preclinical data. *CNS Drug Rev*. 2007;13(1):43-56. doi:10.1111/j.1527-3458.2007.00004.x.

7. Thompson K, Pohlmann-Eden B, Campbell LA, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury. Thompson K, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2015;26(8):1–83.

8. Carney N, Totten A, OReilly C, Ullman J, Hawryluk G, Bell M, et al. Guidelines for the Management of Severe Traumatic Brain Injury. Vol. 1. 2016 Sep pp. 1–244.

9. Szaflarski JP. Is There Equipoise Between Phenytoin and Levetiracetam for Seizure Prevention in Traumatic Brain Injury? Epilepsy Currents. 2015 Mar 22;15:94–7.

10. Huijben JA, Volovici V, Cnossen MC, Haitsma IK, Stocchetti N, Maas AIR, et al. Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. Critical Care; 2018 Apr 9;:1–9.

11. National Collaborating Centre for Acute Care. Head Injury: triage, assessment, investigation and early management of head injury in infants, children and adults (Partial Update) National Collaborating Centre for Acute Care Guideline commissioned by the National Institute of Health and Clinical Excellence Aug 2007. 2007. pp. 1–448.

12. Mee H, Kolias AG, Chari A, et al. Pharmacological management of post-traumatic seizures in adults: current practice patterns in the UK and the Republic of Ireland. *Acta Neurochir (Wien)*. 2019;161(3):457-464. doi:10.1007/s00701-018-3683-9

13. Avery KNL, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ Open. 2017 Feb 3;7(2):e013537–12.

14. Yaari Y, Selzer ME, Pincus JH. Phenytoin: Mechanisms of Its Anticonvulsant Action. Ann Neurol. 1986 Jan 23;20(2):171–84.

15. French J, Arrigo C. Rapid Onset of Action of Levetiracetam in Refractory Epilepsy Patients. Epilepsia. 2005 Jan 23;46(2):324–6.

16. Nicolson A, Lewis SA, Smith DF. A prospective analysis of the outcome of levetiracetam in clinical practice. Neurology. 2004 Jan 23;63:568–70.

17. Nowack A, Malarkey EB, Yao J, Bleckert A, Hill J, Bajjalieh SM. Levetiracetam reverses synaptic deficits produced by overexpression of SV2A. PLoS One. 2011;6(12):e29560. doi: 10.1371/journal.pone.0029560. Epub 2011 Dec 29. PubMed PMID: 22220214.

18. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Apr 9;20(10):1727–36.

19. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based costeffectiveness analysis: the importance of controlling for baseline utility. Health Econ. Wiley-Blackwell; 2005;14(5):487–96.

20. NICE. Position statement on use of the EQ-5D-5L valuation set. 2017.

21. NICE. NICE Guide to the methods of technology appraisal 2013. 2013. pp. 1–93.

22. Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. PharmacoEconomics. 3rd ed. Springer International Publishing; 2014 Jul 29;32(12):1157–70.

23. Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. BMC Health Serv Res. 2006 Apr 19;6(1):1247–8.

24. Drummond MF, Sculpher MJ, Torrance GW, OBrien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care. 4 ed. New York; 2015. 37 p.