Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE) – an open label randomised controlled trial

Protocol

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CTRC
Clinical Trials Research Centre

NHS
National Institute for Health Research

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PROTOCOL APPROVAL

Authorised by Chief Investigator:

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Signature: _____ **Date:** 16/10/2015

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General Information

This document describes the EcLiPSE (Emergency treatment with Levetiracetam or Phenytoin in Status Epilepticus) trial and provides information about procedures for trial. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Clinical Trials Unit) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator, Dr Richard Appleton, via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment, treatment and follow up will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Liverpool Trials Collaborative (LTC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The Clinical Trials Research Centre (CTRC; http://www.ctrc.org.uk/) is a partner of the LTC collaborative. CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Clinical Trials Unit; MC CTU; CTU), epilepsy, infection, oral health and obstetrics and gynaecology. All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

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The contact details of other individuals involved in the trial are detailed in the Trial Oversight Committee Membership document.

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Glossary

AE	Adverse Event
ALSG	Advanced Life Support Group
APLS	Advanced Paediatric Life Support
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CSE	Convulsive Status Epilepticus
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
ED	Emergency Department
GP	General Practitioner
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
MC CTU	Medicines for Children Clinical Trials Unit
MREC	Main Research Ethics Committee
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIHR HTA	National Institute for Health Research Health Technology Assessment programme
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse[1]
RSI	Rapid Sequence Intubation
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

Status epilepticus – lay definition

Most epileptic seizures and convulsions in children last less than three minutes and will stop by themselves. However, sometimes the seizure will last longer than three minutes. When a seizure has lasted more than five minutes it may not stop and may become what is called convulsive status epilepticus (CSE). This is a medical emergency. To prevent CSE from happening children are given a medicine called a rescue or emergency medicine. The rescue medicine is usually given if the seizure or convulsion has not stopped after five minutes.

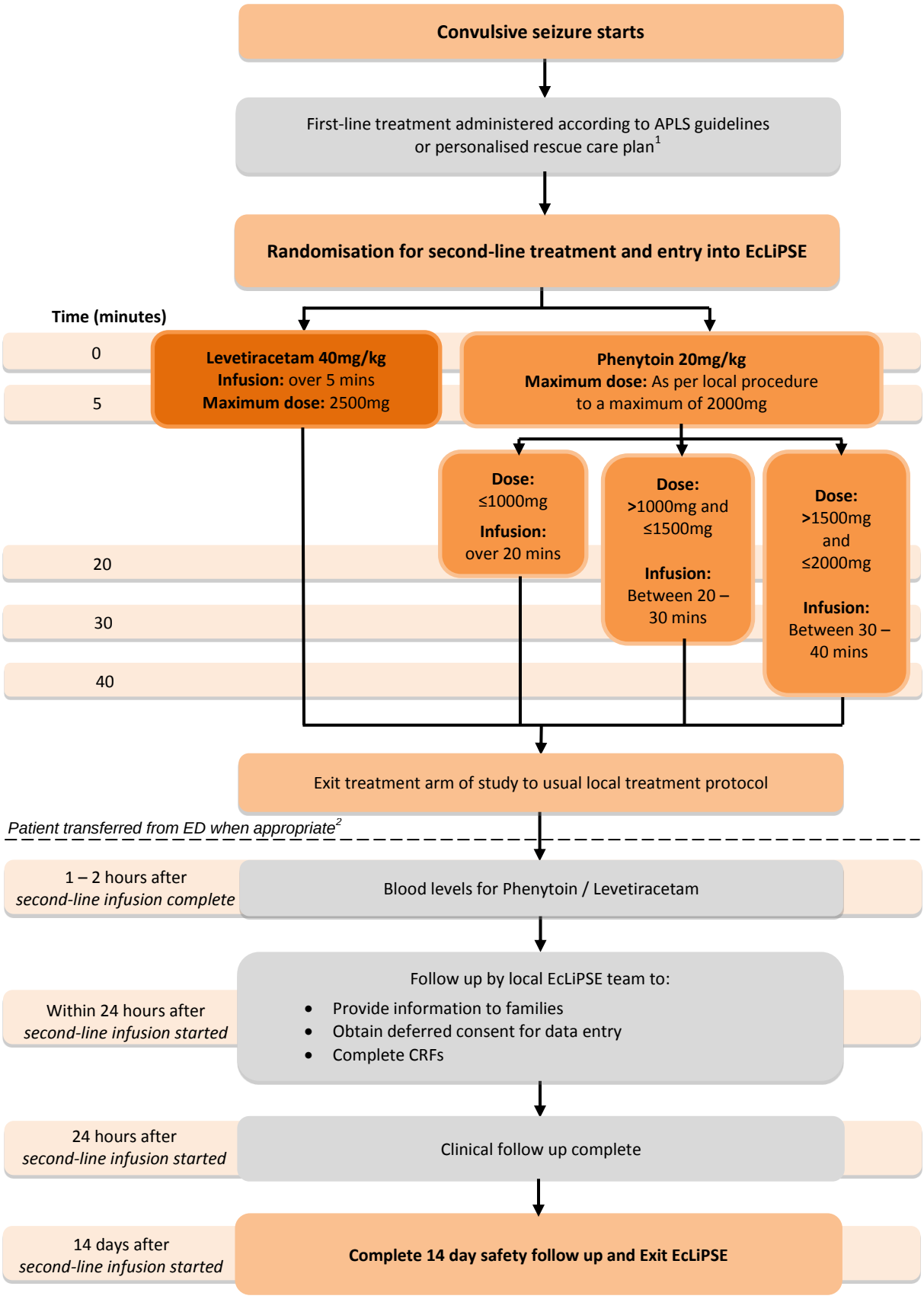
[1] When RN is referred to in this protocol it means either the research nurse or other designated person at site who has been delegated tasks appropriate to this role

1 PROTOCOL SUMMARY

Title:	EcLiPSE: **E**mergen**c**y Treatment with **L**evet**i**racetam or **P**henytoin in **S**tatus **E**pilepticus in Children
Phase:	IV
Population:	The trial will be inclusive of all males and females aged 6 months to 18 years, who present with convulsive status epilepticus that fails to respond to first-line treatment. Children with absence or myoclonic status, non-convulsive status epilepticus or infantile spasms or those who have a known contraindication to the use of the trial medications are excluded.
Study Centres and Distribution:	EcLiPSE will run in approximately 25-30 emergency departments (EDs) in NHS secondary and tertiary hospitals in the UK.
Study Duration Per Participant:	14 days
Description of Agent/ Intervention:	Eligible children will be randomised to receive either intravenous levetiracetam 40mg/kg or intravenous phenytoin 20mg/kg.
Primary Endpoint:	Time to cessation of all visible signs of convulsive seizure activity.
Secondary Endpoints:	1. Need for further anticonvulsant(s) to manage the seizure after the initial agent. 2. Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol). 3. Need to be admitted to critical care. 4. Serious adverse reactions including death, airway complications, and cardiovascular instability (cardiac arrest, arrhythmia and hypotension requiring intervention), extravasation injury ('purple-glove syndrome'), extreme agitation.

Protocol Summary - continued

Schematic of Study Design



[1] *Administration of the first-line treatment may have occurred prior to arrival in the ED.*
[2] *If a patient is randomised but **not** treated with a second-line anticonvulsant follow up would end at this point.*

2 BACKGROUND INFORMATION

2.1 Introduction

Convulsive status epilepticus (CSE) is the most common neurological, serious and life threatening medical emergency in children. The estimated incidence is at least 20 per 100,000 children per year (1, 2). The annual report of the Paediatric Intensive Care Audit Network identified CSE as the fourth most common cause for PICU admission in the UK between 2007-2009 accounting for 5.6% of all PICU admissions. These children are also at increased risk of mortality and irreversible morbidity, including chronic drug-resistant epilepsy, neurodisability and learning difficulties (3) which may be related to not only the cause and duration of CSE, but also its management. Both chronic, drug-resistant epilepsy and neurodisability frequently result in major and long-term demands on both acute and chronic NHS and other community resources.

Improvements in second-line anticonvulsants will reduce the demand for intensive care admission and long-term morbidity associated with CSE.

2.2 Rationale

The current UK-wide 'emergency care pathway' for the management of acute tonic-clonic seizures and CSE in children is that adopted by the Advanced Life Support Group (ALSG) using the Advanced Paediatric Life Support (APLS) guideline (4). The APLS uses phenytoin as the first-choice second-line 'control' or 'standard' anticonvulsant and is administered if the child's seizure has not responded to two doses of a benzodiazepine. If the child is allergic to phenytoin (previous serious adverse event) or has not responded to this anticonvulsant previously, phenobarbital will be administered (this is rare). For the few children who are already receiving phenytoin as an oral maintenance anticonvulsant, they will usually be given intravenous phenytoin as the first-choice second-line 'control' or 'standard' anticonvulsant. The reason for this is because in this situation the most likely cause of the prolonged tonic-clonic seizure will be a low blood level of phenytoin.

Phenytoin has been the standard intravenous anticonvulsant in the treatment of CSE since the 1940s. However, there is minimal evidence to support its effectiveness for this indication. There is more literature on its potential adverse effects, particularly on the cardiovascular system and skin, including specifically the purple-glove syndrome. Because of these it is infused through a large vein over at least 20 minutes with continuous ECG and blood pressure-monitoring. Too rapid an infusion may result in cardiac arrhythmias and cardiac arrest. Following the termination of CSE the drug is rarely used as a maintenance oral anticonvulsant because of its complex pharmacokinetics which may result in toxicity or loss of effect, with subsequent need for frequent monitoring of blood levels. It may interact with many other drugs (including many other anticonvulsants) and give rise to long-term cosmetic effects (facial hair and coarsening of facial features), and is implicated in increased risk of osteoporosis and high risk of teratogenesis on the developing foetus. Consequently in routine clinical practice following the use of intravenous phenytoin to terminate CSE, patients who require a maintenance anticonvulsant will be started on a different drug; this will usually be carbamazepine, levetiracetam or sodium valproate depending on the type of seizures. Carbamazepine cannot be administered intravenously,

unlike levetiracetam and sodium valproate. Concerns have been expressed over the use of sodium valproate because of its adverse safety profile, particularly on liver function, weight gain and teratogenicity.

Levetiracetam is a relatively new anticonvulsant which has been used in the UK and the rest of Europe for 10 years. It is available in oral (tablet and suspension) and intravenous preparations. Considerable anecdotal and limited randomised controlled trial data (against a benzodiazepine, lorazepam) and more than exists for phenytoin for this clinical indication, suggest that this anticonvulsant is effective in the management of acute tonic-clonic seizures (including CSE) and is associated with very few adverse effects. The drug can be infused over 5-7 minutes and does not cause hypotension, cardiac arrhythmias or extravasation into the skin ('purple glove syndrome') which may occur with phenytoin. The faster infusion rate (5-7 minutes rather than 20-25 minutes) means that theoretically the seizure will terminate more rapidly. Finally for those patients that require long-term oral maintenance treatment following the episode of status epilepticus, it is easy to continue with oral levetiracetam because this is not associated with the pharmacokinetic and long-term adverse effects of phenytoin. Current evidence indicates that levetiracetam does not interact with other drugs (including other anticonvulsants) and is not associated with liver failure, osteoporosis or significant risk of teratogenicity (as occurs with phenytoin or sodium valproate).

The management of CSE is based on a national algorithm using a stepwise approach (4). The initial step is two doses of a benzodiazepine and if the child continues to convulse a first-choice second-line (usually longer-acting) anticonvulsant is administered (4). There is some evidence to support the choice of the initial benzodiazepine (5, 6) but almost no randomised controlled trial (RCT) evidence to support the use of phenytoin as the second-line anticonvulsant. Extremely limited evidence suggests that phenytoin will terminate CSE in 50-60% of cases (7). Failure of phenytoin necessitates rapid sequence induction, intubation, and transfer to the intensive care unit; these patients may also suffer iatrogenic consequences of this level of care, including pneumonia, hospital-acquired infections and prolonged admission (4). Adverse events associated with phenytoin include hypotension, cardiac arrhythmias (which may result in death), hepatotoxicity, phlebitis, severe tissue extravasation injury (resulting in 'purple glove syndrome') and Stevens-Johnson syndrome (which may also be fatal). In addition, there are well-recognised practical difficulties with the continued use of phenytoin in the immediate post-acute situation. These include the need to routinely monitor blood levels of the drug, the risk of significant interactions with other drugs (causing significant changes in blood levels of phenytoin resulting in either toxicity or poor anticonvulsant effect) and on-going concerns over cardiac arrhythmias and hypotension if the drug continues to be administered intravenously.

Intravenous levetiracetam appears to be safe and effective in treating adults and children with convulsive and non-convulsive status epilepticus, and those with acute repetitive seizures (8-15). Its success rate varies between 76 and 100% (8-16). A recently published randomised study of the initial intravenous treatment of CSE in adults reported seizure cessation rates of 76.3% (levetiracetam) and 75.6% (lorazepam, a benzodiazepine) (16). There have been no reports of cardiac arrhythmias, hypotension, tissue extravasation reactions, Stevens-Johnson syndrome or hepatotoxicity with the use of intravenous levetiracetam. Mild, and usually transient, sedation and agitation have been reported only

infrequently following intravenous levetiracetam. Consequently, this anticonvulsant may be more effective and safer than the 'standard' first-choice second-line anticonvulsant, phenytoin. Loading doses of intravenous levetiracetam have ranged from 20 to 60 mg/kg (17). The highest loading dose of 60mg/kg has been extrapolated from adult studies. A previous open study of over 60 children from the UK reported a loading dose of 20 or 30 mg/kg (15) with no significant adverse side-effects and a recently-established RCT in the USA, the 'Established Status Epilepticus Trial 2013' (18) uses a loading dose of 60mg/kg.

This growing body of evidence therefore suggests that levetiracetam should be considered as a replacement for phenytoin as the first-choice second-line anticonvulsant for use in the treatment of CSE following the failure of a benzodiazepine (8, 19, 20). This hypothesis must now be tested, and support for an RCT has been highlighted in a recent systematic review (21). Importantly, research in the management of CSE was cited as one of five priority areas in the partial update of the Epilepsy Guideline published by National Institute for Health and Care Excellence (NICE) in January 2012 (22).

This study aims to provide the first (unique) RCT evidence of the efficacy and safety of a first-choice second-line anticonvulsant for CSE in children.

2.3 Objectives

1. To determine whether intravenous phenytoin or intravenous levetiracetam is the more efficacious second-line anticonvulsant for the emergency management of convulsive status epilepticus (CSE) in children.
2. To determine if intravenous levetiracetam is associated with fewer adverse effects than intravenous phenytoin.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

The standard first-choice second-line anticonvulsant for CSE (phenytoin) only terminates prolonged tonic-clonic seizures in 50-60% of cases. Phenytoin must be infused slowly over a minimum of 20-25 minutes to avoid the risk of hypotension and cardiac arrhythmias. It may also cause irritation of veins with a chemical phlebitis, and extravasation of the drug may cause soft tissue inflammation, which in the most extreme case, may cause the 'purple glove syndrome'. Consequently the risks associated with phenytoin include lack of effectiveness and significant adverse effects. There are only very limited RCT data on the effectiveness of levetiracetam. There are also very limited reports of adverse effects associated with intravenous levetiracetam; these have included dizziness, somnolence and headache (17, 23). If intravenous levetiracetam is less effective than phenytoin, this could prolong the child's episode of CSE. However, because the management of all children with CSE is based on a national time-driven protocol (algorithm) designed by the Advanced Paediatric Life Support (APLS) group, all children in whom CSE is not terminated by the randomised treatment (levetiracetam or phenytoin) will then receive the next treatment step as per this algorithm (4).

2.4.2 Known Potential Benefits

Predominantly anecdotal evidence suggests that levetiracetam may terminate CSE in >70% of cases. The reported adverse effects following the infusion of even high doses of intravenous levetiracetam (60mg/kg/day) are infrequent and mild (17). Consequently, the potential benefits are that levetiracetam may be more effective, safer, or both, than intravenous phenytoin in terminating prolonged tonic-clonic seizures.

3 SELECTION OF CENTRES/CLINICIANS

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in the supplementary document 'EcLiPSE Centre Assessment Criteria'.

Initiation of centres will be undertaken in compliance with CTRC SOPs TM017 and TM018; Centres fulfilling the criteria will be selected to be recruitment centres for the EcLiPSE trial and will be opened to recruitment upon successful completion of all global (e.g. MREC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to CTU as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the 'EcLiPSE Participating Centres' log, maintained separately to the protocol.

4 TRIAL DESIGN

4.1 Primary Endpoint

Time to cessation of all visible signs of convulsive seizure activity*.

4.2 Secondary Endpoint(s)

1. Need for further anticonvulsant(s) to manage the seizure after the initial agent.
2. Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE.
3. Need to be admitted to critical care.
4. Serious adverse reactions including death, airway complications, and cardiovascular instability (cardiac arrest, arrhythmia and hypotension requiring intervention), extravasation injury ('purple-glove syndrome'), extreme agitation.

***Defined as:**
Time to cessation of all visible signs of convulsive seizure activity will be calculated from the time of randomisation. A secondary analysis will use time from the start of the infusion.

Children who present with convulsive status epilepticus may show some features that resemble seizure activity even after the cessation of overt convulsive seizures. These include staring, irregular myoclonic or brief clonic jerks, oromotor automatisms or unresponsiveness. **Repeated, rhythmic clonic movements will be considered as representing ongoing seizure activity.**

4.3 Internal Pilot

The trial will include an 18 month internal pilot involving five centres; however additional centres will be opened during this period.

The 18 month internal pilot will enable the five centres involved to be opened, be fully up to speed with trial procedures, and be achieving the optimal recruitment rate (assumed to be achieved 3 months after opening). This time frame will also allow each site a minimum of 6 months of active recruitment at the optimal level to demonstrate their recruitment rates and allow us to predict trial activity into the main phase of the trial.

Success criteria of the pilot are based upon:

(A) Recruitment

(1) If the predicted recruitment period is 36 months or less, proceed to main trial.

(2) If the predicted recruitment period is between 36 months and 48 months, consider and introduce ways to reduce this e.g.
   a. increase the number of centres
   b. address training needs
   c. determine whether new evidence suggests eligibility criteria could be widened.

   Then proceed to main trial with amendments.

(3) If the predicted recruitment period is more than 36 months, and no obvious solutions exist, abandon the plan for the main trial.

(B) Deferred consent

(1) If the deferred consent rate is 80% or more, proceed to main trial.

(2) If deferred consent rate is between 60% and 80%, and there is no clear association between provision of deferred consent and the child's outcome, then analyse reasons why patients/guardians do not want to participate to identify any aspects amenable to change. Then proceed to main trial as amended.

(3) If deferred consent is less than 60%, analyse reasons why patients/guardians do not want to participate. If consent declination is associated with poor patient outcome e.g. death, abandon the main trial.

(C) Completeness of primary outcome data

(1) If primary outcome data are available for over 90% of randomised and consented participants, proceed to main trial.

(2) If primary outcome data are available for 70-90% of randomised and consented participants, analyse reasons for missing data and identify whether any aspects are amenable to change. Then proceed to main trial as amended.

(3) If primary outcome data are available for less than 70% of participants randomised and consented, abandon the plan for the main trial.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Males and females aged 6 months to 18 years (<18th birthday).
2. Presenting seizure is generalised tonic-clonic, generalised clonic or focal clonic status epilepticus that requires second-line treatment to terminate the seizure.
3. First-line treatment administered according to APLS guidelines or the child's personalised rescue care plan in order to try and terminate the presenting seizure.

Eligibility Notes

- APLS guidelines:
  Guidelines classify two doses of benzodiazepines as first-line treatment. If patients are given more than two doses of benzodiazepines then they are still eligible.

- Personalised rescue care plan:
  Patients whose personalised rescue care plan includes rectal paraldehyde as the first-line treatment are still eligible.

- Maintenance anti-epileptic medication:
  Patients receiving oral phenytoin or levetiracetam as part of their regular oral anti-epileptic drug regime are still eligible for this trial.

5.2 Exclusion Criteria

1. Absence, myoclonic or non-convulsive status epilepticus, or infantile spasms.
2. Known or suspected pregnancy.
3. Known contra-indication or allergy to levetiracetam or phenytoin. This includes where the child's personalised rescue care plan states that the child never responds to, or has previously experienced a severe adverse reaction to, phenytoin, levetiracetam, or both.
4. Known renal failure (patients on peritoneal or haemodialysis or with renal function <50% expected for age)
5. Previous administration of a second-line antiepileptic drug prior to arrival in the emergency department.
6. Known to have previously been treated as part of EcLiPSE.

6 RECRUITMENT AND RANDOMISATION

6.1 Screening

Screening information on patients who are assessed for eligibility (whether or not they consent or are randomised) will be collected by the completion of a participant screening form. These screening forms will provide important information for monitoring purposes and possible reasons for non-randomisation.

Screening will commence once a child has arrived in the ED and has started first-line treatment.

6.2 Recruitment

Patients aged 6 months to 18 years presenting to the emergency department (ED) with generalised tonic-clonic, generalised clonic or focal cloned status epilepticus that requires second-line treatment will be assessed by clinical staff and randomised if they fulfil the eligibility criteria (see section 5).

For the reasons described in section 11.1, **no** attempt will be made to obtain fully informed consent for the trial from the participant/parent/legal representative prior to randomisation. Please see section 6.4 for the deferred consent procedures.

After randomisation, if written deferred consent is provided, the patient will be followed-up in the trial and the RN will collect the clinical and laboratory data required from clinical records (see section 8). If participant/parent/legal representative consent is not provided, the consent tracking CRF should be completed (see section 6.4.12).

Death in the emergency department, or within 24 hours of presentation, is a very rare occurrence for the patient group eligible for EcLiPSE. However if required, please refer to section 6.4.9 for the deferred consent procedure for bereaved families.

6.3 Randomisation

Centres will be provided with a series of sequentially numbered EcLiPSE randomisation packs to be stored in an appropriate secure location within the ED for ready access upon presentation of eligible patients.

Randomisation packs are brown cardboard tamperproof A4 envelopes. The construction is resistant to accidental damage or tampering and contents cannot be viewed without fully opening.

Each pack is sequentially numbered and when randomising the next sequentially numbered pack should be used.

The CRFs which need to be completed at the patient bedside while in the ED are contained within the randomisation pack. These will be prepopulated with the centre code, participant randomisation number and randomly allocated treatment.

The randomisation pack should be opened once eligibility has been confirmed on the screening form. However, ED staff should ensure there is sufficient time to prepare the randomised treatment for infusion when required.

If the participant has been randomised but the seizure terminates prior to infusion of the randomly allocated treatment then the patient may **still be treated with the randomised treatment allocation** should the participant's seizure re-start while they remain in the ED.

If the randomised treatment is **not administered** whilst the participant is in the ED, the participant will still be considered as recruited and the randomisation number will apply. The treatment administered (if any) will be recorded on CRF form 1, along with reasons why it was not possible to treat as per allocation. The participant will be followed up as detailed in section 8.1.

The RN will periodically check to ensure that the correct number of randomisation packs is present, that they are intact and that the sequential numbering system is maintained. Any discrepancies will be immediately reported to the CTU. The RN will also ensure that there are adequate stocks of trial treatments and will liaise with the local pharmacy department as necessary.

6.4 Deferred Consent

Deferred consent and assent (if applicable/appropriate) will be sought for all randomised participants.

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. When consent is deferred, an individual is agreeing to the use of data that had already been collected for trial purposes and for continued participation in the trial. In obtaining and documenting deferred consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

6.4.1 Approaching Parents/Legal Representatives/Participants

The RN, or other designated member of the research team at site, will be notified of the randomisation and will approach participant/parent/legal representative to seek deferred consent as soon as possible after completion of trial treatment (ideally within 24 hours of randomisation).

Before approaching the participant/parent/legal representative, the RN will check with the relevant ward staff that the participant is stable and that timing is appropriate. If the participant's condition has not stabilised additional time should be allowed before approaching parent/legal representative. If the participant has died please refer to section 6.4.9.

6.4.2 Providing Trial Information

The RN, or other designated member of the research team at site will first approach the participant/parent/legal representative to seek verbal permission for an audio recording of the study discussion to occur, if applicable, see section 8.5.1 for further details).

The RN, or other designated member of the research team at site will explain to participant/parent/legal representative the reasons why deferred consent is used emergency care research.

Staff will also discuss with the participant/parent/legal representative the:

- Objectives
- Risks and inconveniences of the trial
- Conditions under which it is to be conducted
- Emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason.

The participant/parent/legal representative will be provided with the appropriate Patient Information and Consent/Assent forms (see section 6.4.4 and 6.4.5 for consent and assent forms respectively), and will be asked to read and review the document.

Upon reviewing the document, all participants will be given opportunity to ask any questions that may arise, have the opportunity to discuss the study with their surrogates and have time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

Participants/Parents/legal representatives should decide whether or not to join the trial ideally within 24 hours of randomisation or before their child/relative is discharged from hospital.

6.4.3 Consent/Assent Form Completion

If the participant/parent/legal representative decides to participate in the trial they will be asked to sign and date the age appropriate EcLiPSE consent/assent form (see section 6.4.4 and 6.4.5 for consent and assent forms, respectively).

The participant/parent/legal representative will personally sign and date the consent/assent form. Once the participant/parent/legal representative has signed the consent/assent form, the person obtaining consent/assent must then personally sign and date the form.

A copy of the fully completed consent/assent form will be given to the participant/parent/legal representative for their records. The original copy will be filed in the participant's medical notes. Copies of the consent/assent form should also be sent to the CTU.

Once the deferred consent form has been completed, parents/legal representatives will be provided with the Consent Study Parent/Legal representative Questionnaire to complete. See section 8.5.2 for further details.

6.4.4 Information Sheets and Deferred Consent Forms

The applicable consent form below should be completed in order for trial follow up to occur:

Trial Participant Status	Deferred Consent Documentation to be Completed	Completed by
Minors – All children and young people aged less than 16 years	EcLiPSE Parent/legal representative information sheet and deferred consent form (On-site) ***Or*** *EcLiPSE Parent/legal representative information sheet and deferred consent form (Home) (see section 6.4.10)*	Researcher and: i. A parent or person with parental responsibility. ii. Personal legal representative* iii. Professional legal representative*
Adults (aged 16 to 18 years) who, upon recovery from their seizure, **do not have** capacity to give informed consent ("incapacitated adults")	EcLiPSE Parent/legal representative information sheet and deferred consent form (On-site) ***Or*** *EcLiPSE Parent//legal representative information sheet and deferred consent form (Home) (see section 6.4.10)*	Researcher and: i. Personal legal representative* ii. Professional legal representative*
Adults (aged 16 to 18 years) who, upon recovery from their seizure, **have** capacity to give informed consent	EcLiPSE Adult information sheet and deferred consent form (16-18 years) (On-site) ***Or*** *EcLiPSE Adult information sheet and deferred consent form (16-18 years) (Home) (see section 6.4.10)*	Researcher and trial participant

*****Please refer to section 6.4.7 for definitions of legal representatives.

Note: If the participant dies prior to deferred consent being sought instead refer to section 6.4.9.

6.4.5 Assent Information Sheets and Deferred Assent Forms

In conjunction with informed consent for minors, the applicable assent form should be completed, where capacity allows:

Trial Participant Status	Deferred Assent Documentation to be Completed	Completed by
Minors – Children aged 6 to 10 years	EcLiPSE Child information sheet and deferred assent (6-10 years)	Researcher, parent/legal representative* and trial participant
Minors – Children aged 11 to 15 years	EcLiPSE Young person information sheet and deferred assent (11-15 years)	Researcher, parent/legal representative* and trial participant

*****Please refer to section 6.4.7 for definitions of legal representatives.

6.4.6 Incapacitated Adults and Minors

Participants who do not have capacity to give informed consent or assent may still be provided with information about the trial. The appropriate information sheet should be selected that is suitable for the participant's stage of development and level of understanding:

- EcLiPSE Child information 6-10 years no capacity for assent
- EcLiPSE Young person information sheet 11-15 years no capacity for assent
- EcLiPSE Adult information sheet 16-18 years incapacitated adult.

6.4.7 Definitions of Legal Representatives

England and Wales:

- Personal legal representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so. If one is not available:
- Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

Scotland:

- Personal legal representative i.e.
    - Adult's Welfare Guardian or Welfare Attorney, or if not appointed:
    - The adult's nearest relative, if neither are reasonably contactable:
- Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

6.4.8 Adults Who Gain Capacity during the Course of their Participation

The consent given by an appropriate legal representative on behalf of an adult lacking capacity to do so for themselves shall represent the presumed will of the incapacitated adult and as such it is not mandatory to re-approach adults recruited in such a manner should they regain their capacity to give consent during the course of their participation in EcLiPSE.

Legal representatives will be made aware that, should this circumstance arise during the trial participation period (24 hours), the adult will be provided with information about EcLiPSE but will not be approached to provide their own consent. The adult participant will be made aware that they can withdraw from the trial at any time by revoking the informed consent provided by their legal representative.

6.4.9 Death Prior to Deferred Consent being sought

This is likely to be a very rare occurrence. However, when a participant dies before deferred consent has been sought, the attending RN will obtain information from colleagues and bereavement counsellors to establish the most appropriate practitioner to notify parents/legal representative of the research involvement.

Deferred consent can be sought from parents/legal representatives following the death of their child/relative and prior to the parents/legal representative's departure from the hospital. However, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Parent/Legal representative information sheet and deferred consent form (B-On-site) would be used.

If deferred consent is not sought prior to the parent/legal representative's departure from hospital then the parents/legal representative will be notified by being sent a personalised letter from the most appropriate practitioner (Parent/Legal representative bereavement letter no. 1), and a copy of the Parent/Legal representative information sheet and deferred consent form (B-Home). Both will be sent by post 4 weeks after randomisation. Where possible this practitioner should already be known to the family. The letter will explain the EcLiPSE trial, reasons for deferred consent, how to opt in or out of the trial and provide contact details if parents wish to discuss the study with a member of the research team (either in person or by telephone).

If after 4 weeks after sending the initial letter to the bereaved family, there is no response, a follow up letter (Parent/Legal representative bereavement letter no. 2) along with the Parent/Legal representative bereavement information sheet and consent form (B-Home) will be sent to the bereaved family. This second letter will again explain the EcLiPSE trial, reasons for deferred consent, how to opt in or out of the trial and provide contact details if parents wish to discuss the study with a member of the research team (either in person or by telephone). In addition, this letter will also confirm that if no consent form is received within 4 weeks of the letter being sent then the participants' data will be included in the trial, unless the family notify the site team otherwise.

In the cases where a consent form is not returned, the consent tracking CRF which documents dates of communication, will document the consent process and will act as evidence of consent.

In addition, all deaths should be reported on a Serious Adverse Event CRF and faxed to the CTU within 24 hours (see section 10).

6.4.10 Discharge/Transfer Prior to Deferred Consent being sought

It is expected that deferred consent is sought for **all** participants prior to discharge/transfer to another hospital (if the participant dies prior to consent being sought instead refer to section 6.4.9). However, in the rare instances where deferred consent is not sought prior to discharge/transfer the following should occur:

The RN, or other designated member of the research team at site, will call the participant/parent/legal representative within 5 working days of randomisation to inform the family of the participant's involvement in the trial and provide details of the trial as per section 6.4.2.

Note: Audio-recordings of telephone discussions are not required.

Once the telephone call has been completed, the RN, or other designated member of the research team at site, will post as applicable:

- A covering letter:
  - Parent/Legal Representative covering letter to home or;
  - Adult covering letter to home.
- Information leaflet and consent form:
  - Parent/Legal presentative information sheet and consent form (Home) or;
  - Adult information sheet and consent form (Home).
- The Consent Study Parent/Legal representative questionnaire (for Parents/Legal representatives only).

The covering letter will confirm that the Adult/Parent/Legal representative has 4 weeks from the date of the letter to return the consent form confirming whether they would like to participate in the trial or not. The letter will also explain the reasons for, and benefits of completing the enclosed questionnaire (if applicable).

If no response is received within 4 weeks, the covering letter will confirm that the participant will automatically be included within the trial.

In the cases where a consent form is not returned, the consent tracking CRF which documents dates of communication, will document the consent process and will act as evidence of consent.

6.4.11 Patients randomised but not treated with second-line treatment in the ED

Consent for data collection whilst in the ED should be sought using the same processes that are detailed above. However, the following information sheet and consent form (as applicable) should be used instead:

- Adult/Parent/Legal Representative information sheet (NT)
- Adult/Parent/Legal Representative consent form (NT-on-site)
- Adult/Parent/Legal Representative consent form (NT-home)

Note: As only minimal data will be collected for these patients (data to be collected; demographics, details of admission, seizure type and reason randomised treatment not given), information sheets do not need to be provided for incapacitated participants and assent forms do not need to be completed for participants aged 6-15 years.

The questionnaires, audio-recordings of consent discussions and interviews relating to the consent study are also not applicable for these participants.

6.4.12 Deferred Consent Declined

If deferred written informed consent is declined by the appropriate participant/parent/legal representative the consent tracking CRF* should be completed.

***Note:** The trial consent form filled in by the adult/parent/legal representative. The consent tracking CRF is a separate trial document completed by the RN and records whether consent was obtained and reasons for non-consent if applicable (where provided).

6.5 Patient Discontinuation and Withdrawal

6.5.1 Discontinuation

If a patient continues to experience seizures despite the completion of the trial intervention they would be treated with additional anticonvulsants as per the local protocol for the treatment of convulsive status epilepticus. These treatments would be recorded as these data constitute some of the secondary outcomes of this trial. This would **not** necessitate the patient discontinuing the study.

6.5.2 Withdrawal of Consent

Generally, follow-up will continue unless the participant/parent/legal representative explicitly withdraws consent for follow-up.

The participant/parent/legal representative is free to withdraw consent at any time without providing a reason and without being subject to any resulting detriment. The rights and welfare of the patients will be protected by emphasising to them throughout the trial that the quality of medical care will not be adversely affected if they decline to participate in the study.

Where the participant/parent/legal representative wishes to withdraw consent there will be clarification whether this is withdrawal of consent for data already collected or for future data collection. A withdrawal CRF should be completed documenting the type and reason for withdrawal. Centres should explain the importance of remaining in trial follow-up. Failing this they should be informed of the importance of contributing data.

6.5.3 Participant Transfers

The short duration of this trial obviates the need for participants to be followed up after discharge from the treating centre. A minority of participants will be transferred in from another hospital and will be treated with the study medication. All of these participants are highly likely to be admitted to the treating hospital for a minimum of 24-48 hours prior to either transfer back to their original (referring) hospital or discharge home. The required primary and secondary outcome data will be collected during the first 24 hours and prior to transfer or discharge.

7 TRIAL TREATMENT/S

7.1 Introduction

This study is a phase IV, multi-centre, parallel group, randomised controlled, open label trial comparing levetiracetam with phenytoin for the treatment of convulsive status epilepticus in children and young people. The following drugs are Investigational Medicinal Products (IMPs) in this trial:

- Levetiracetam 100mg/ml concentrate for solution for infusion
- Phenytoin Sodium 50mg/ml Solution for injection

The provision of both IMPs is the responsibility of each individual participating site in accordance with standard clinical practice.
Participants will be randomised to one of the following treatment arms:

Arm A: Levetiracetam 40mg/kg (maximum 2500mg)
Infusion location: In a large vein
Infusion time: 5 minutes
Concentration: A maximum of 50mg/ml with sodium chloride 0.9%.

Arm B: Phenytoin 20mg/kg (maximum 2000mg)
Infusion location: In a large vein
Infusion time for dose ≤1000mg: 20 minutes
Infusion time for dose >1000mg and ≤1500mg: Between 20 - 30 minutes
Infusion time for dose >1500mg and ≤2000mg: Between 30 – 40 minutes
Concentration: A maximum of 10mg/ml with sodium chloride 0.9%.

Treatment will constitute a single dose of the randomised allocated treatment administered via intravenous infusion. The dosage to be administered will be based on the actual or estimated weight of the participant. In cases of weight estimation, this will be performed using APLS guidance.

If seizures persist at the end of the IMP infusion, further medical management should be decided by the local team in accordance with the national APLS pathway and will be independent of the trial protocol; all children in whom CSE is not terminated by the randomised treatment (levetiracetam or phenytoin) should receive the next treatment step as per the APLS algorithm (4).

7.2 Packaging, Labelling, Storage and Stability

For the purposes of IMP management, the following assertions are made:

1. EcLiPSE is an open label trial which uses investigational medicinal products with marketing authorisation in the UK,
2. Both levetiracetam and phenytoin injection are being used without the need for further manufacturing or packaging processes.

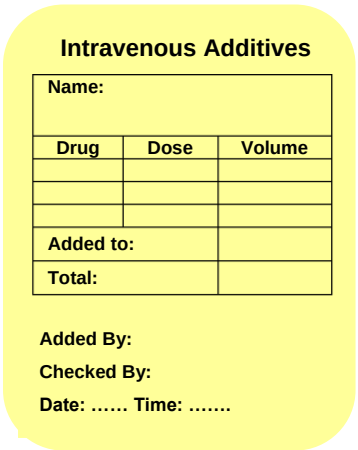
3. Although trial randomisation determines the treatment to be administered, the treatments utilised in this protocol are UK market authorised products constituting standard care.
4. Trial treatments will be administered to a participant in accordance with a written direction on a standard hospital prescription chart given by a healthcare professional.

5. Trial treatments will be prepared and administered immediately upon randomisation in the ED and:
    a. The allocated treatment will be removed from non-IMP stock within the ED
    b. The allocated treatment does not become an IMP until it is removed from its outer packaging.
6. In line with routine clinical practice, the preparation and administration of the treatment will be independently checked by two trained authorised personnel.
7. The prepared trial treatment will be labelled using Trust approved "intravenous additive label" (including, but not limited to, patient name, name of drug, time of preparation) at the point of preparation in accordance to individual Trust policies.

As such:

1. Temperature monitoring should be in line with local requirements for the general medicine supplies held in the ED for routine care.
2. Although EDs should ensure adequate stocks of both treatments to facilitate recruitment, ring fenced IMP stock is not necessary.
3. The provisions of Regulation 46(2) of SI 2004/1031 apply to both IMPs; trial-specific (Annex 13) labelling is therefore not required and a Trust approved "intravenous additive label" (including, but not limited to, patient name, name of drug, time of preparation – see example below) is applied to the prepared treatment at the point of preparation in accordance to local routine practice.

An example of intravenous additive label which will be added to the IMP in hospital following randomisation:



Intravenous Additives

Name:		
Drug	**Dose**	**Volume**
Added to:		
Total:		

Added By:

Checked By:

Date: …… Time: …….

7.3 Arm A - Levetiracetam

7.3.1 Formulation

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.
An example summary of product characteristics (SmPC) for use as reference safety information is supplied as a document supplementary to the protocol.

Active ingredient	Levetiracetam
Excipients	Refer to SmPC
Pack Size(s)	Refer to local supply chain (local pharmacy)
Route of Administration	Intravenous
Storage temperature / time	Refer to SmPC
Supplier's name	Local supply chain (local pharmacy)

7.3.2 Preparation, Dosage and Administration of Levetiracetam

Levetiracetam should be administered as a **single dose,** at a dosage of **40mg/kg (maximum dose 2500mg)** of body weight (estimated according to the child's age). The treatment should be administered intravenously as an **infusion over 5 minutes** in a large vein.

Levetiracetam should be **diluted to a maximum of 50mg/mL** with sodium chloride 0.9% before administration, which is in line with the New Zealand National Guidelines on the management of convulsive status epilepticus in children (https://www.starship.org.nz/for-health-professionals/starship-clinical-guidelines/s/seizures-status-epilepticus/#Management-algorithm (accessed 18 Aug 15)). Safety data from previous studies showed that there is a slight increase in the rate of pruritus with this concentration but with no significant changes in other safety parameters (13).

7.4 Arm B - Phenytoin

7.4.1 Formulation

Pharmacotherapeutic group: Antiepileptics. ATC code: N03AB 01
An example SmPC for use as reference safety information is supplied as a document supplementary to the protocol.

Active ingredient	Phenytoin sodium
Excipients	Refer to SmPC
Pack Size(s)	Refer to local supply chain (local pharmacy)
Route of Administration	Intravenous
Storage temperature / time	Refer to SmPC
Supplier's name	Local supply chain (local pharmacy)

7.4.2 Preparation, Dosage and Administration of Phenytoin

Phenytoin should be reconstituted in accordance with the manufacturers SmPC.

Phenytoin should be administered as a **single dose,** at a dosage of **20mg/kg (maximum dose 2000mg)** of estimated body weight (estimated according to the child's age).

The **total maximum dose** of phenytoin administered should be **2000mg**. However, sites should confirm prior to study start if their local procedure states that the maximum phenytoin dose is less than 2000mg. If this is the case then the maximum dose for phenytoin should be as per local procedure and should be adhered to.

The treatment should be administered intravenously as an **infusion** in a large vein:

- Infusion time for phenytoin dose ≤1000mg: **20 minutes**
- Infusion time for phenytoin dose >1000mg and ≤1500mg: **Between 20 – 30 minutes**
- Infusion time for phenytoin dose >1500mg and ≤2000mg: **Between 30 – 40 minutes**

The final concentration of phenytoin in the solution for infusion should be a maximum of **10mg/ml** with 0.9% sodium chloride.

7.5 Precautions Required for Study Treatments

Please refer to the relevant SmPC for detailed guidance.

- The mixing of the randomised treatment with other drugs is not recommended except with diluents as described in the relevant SmPC.
- Solutions in which a haziness, discoloration or precipitate develops should not be used.
- Continuous monitoring of the electrocardiogram and blood pressure is essential.
- Cardiac resuscitative equipment should be available.
- The patient should be observed for signs of respiratory depression.
- Because of the risk of local toxicity, infuse as directed in section 7.3.2 or 7.4.2 (as applicable) and directly into a large vein through a large-gauge needle or intravenous catheter.
- Inject sterile saline through the same needle or catheter both before and following the injection or infusion of the randomised treatment to avoid local venous irritation – particularly for phenytoin because of the alkalinity of this drug.

7.6 Accountability Procedures for Study Treatments

Details of the manufacturer, name, form, strength, batch number and expiry date of the administered allocated treatment will be recorded on CRF form 1, along with the dose and duration of infusion. The treatment allocation and treatment administered will also be recorded in the participant's medical notes.

As subject compliance can be fully established in the trial, all used IMP will be disposed of locally immediately following administration in accordance to local requirements.

7.7 Assessment of Compliance with Study Treatments

Treatment with the IMP will be administered under the supervision of a clinician and in a controlled clinical environment; therefore, full assessment of compliance is anticipated in this

trial. Data completed on CRF form 1 will be cross checked to monitor allocation and treatment compliance.

7.8 Concomitant Medications/Treatments

If the patient continues to have seizures following administration of the randomised treatment they should be treated as directed by their local clinician.

7.8.1 Medications Permitted

Benzodiazepines through any route administered to treat the current seizure are allowed before randomisation. Patients on maintenance phenytoin or levetiracetam are not excluded from the trial.

Administration of rectal paraldehyde does not exclude the patient from the trial. This is compliant with current APLS and NICE guidance whereby there is the option to use rectal paraldehyde as a first-line treatment (according to the patient's personalised rescue care plan) or simultaneously with randomised treatment.

7.8.2 Medications Not Permitted/Precautions Required

Administration of a second-line anticonvulsant medication prior to randomisation excludes the patient from the trial (section 5.2).

7.8.3 Data on Concomitant Medication

The following data on Concomitant medication will be recorded:

- Benzodiazepines administered prior to randomisation
- Whether trial participants were on maintenance phenytoin or levetiracetam
- The use of other first-line and second-line drugs to treat the seizure, including paraldehyde.
- If the presenting seizure did not cease, which anaesthetic drug was administered.

7.9 Dose Modifications

No specific dosage modifications are required. If the infusion of the randomised treatment is discontinued prior to administration of the full dose for any reason this will be recorded on the CRF.

7.10 Co-enrolment Guidelines

Given the short duration of participation in EcLiPSE and urgency to treat, it is not envisaged that participants will be recruited into other trials in parallel. However, should co-enrolment issues arise, patients are permitted to enter EcLiPSE whilst participating in another trial. This is providing that the other trial will not impact the EcLiPSE primary endpoint.

Any queries regarding co-enrolment should be discussed with the CTU who will contact the Chief Investigator.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule for Follow-up

Patient randomisation status	Randomised treatment administered	Data to be Collected		
		Whilst in the ED	For 24 hours after second-line infusion started	At 14 days (Safety data only)
Randomised	Yes	✓	✓	✓
	No (Different second-line treatment administered)	✓	✓	✓
	No (No second-line treatment administered)	✓[1]		
Not randomised	N/A	✓[2]		

[1] Only minimal data required for these patients. No adverse events to be reported unless requested in CRF form 1.

[2] If patients arrive in the ED and are administered first line treatment but not randomised, only screening information will be collected via the screening form.

Table 1: Trial Assessments

	Screening/ Randomisation	**Follow-up**		
		1-2 hours *after second-line infusion completed*	**0-24 hours** *after start of second-line infusion*	**14 days** *after start of second-line infusion*
Informed consent (deferred)			X	
Assessment of eligibility criteria	X			
Weight (actual or estimate)	X			
Randomisation	X			
Study intervention	X			
Seizure activity	X		X	
Assessment of adverse events	X		X	
Study intervention compliance/accountability	X			
Laboratory assessments – routine bloods and phenytoin/levetiracetam levels		X		
Review of concomitant medications			X	
Physical examination - symptom-directed*			(X)	
Review of medical history			X	
Review of epilepsy history (age at onset of the epilepsy; epilepsy syndrome)			X	
CRF Completion and data query resolution			X	X
CRF review and sign-off			X	X
14 day safety follow up				X

(X) – As indicated/appropriate.

*This physical examination should include a comment on any focal neurological signs

8.2 Procedures for Assessing Efficacy

8.2.1 Seizure Activity

Efficacy relating to seizure activity will be assessed by recording:

- Time seizure commenced
- Time of administration of IMP
- Time of cessation of IMP
- Time of cessation of all visible signs of convulsive seizure activity.
- The number of further convulsive seizures in the 24 hours after the second-line infusion was started.

8.2.2 Need for Further Intervention

Concomitant treatment will be recorded as surrogates for lack of efficacy of the randomised treatment:

- Need for further anticonvulsant(s) to manage the seizure after or in parallel with the randomised agent.
- Need for RSI with thiopentone or another agent (e.g. propofol).
- Need to be admitted to critical care – and the reason for admission (e.g. ongoing seizure activity, respiratory compromise, general medical condition or for any other reason).

8.3 Procedures for Assessing Safety

Safety will be assessed by:

- The PI or delegated research staff monitoring and reporting all adverse events from randomisation until 24 hours after second-line infusion started (see section 10 for adverse event reporting).
- 14 day follow-up questionnaire: to be completed by patients/parents/legal representatives.
- 14 day hospital follow-up: to be completed by EcLiPSE sites using their hospital records.
- An independent Data and Safety Monitoring Committee (IDSMC) (see section 16 for further details).

8.3.1 14 Day Follow up Questionnaire

The 14 day follow up questionnaire will be provided to patients/parents/legal representatives who are randomised, administered a second-line treatment in the ED and are consented on site.

Prior to providing the questionnaire, the RN will complete the participant (randomisation) number and the date the questionnaire should be completed. The date to be completed is 14 days after the second-line infusion was started. The questionnaire should be provided as soon as written consent has been obtained.

The questionnaire will be explained to the patient/parent/legal representative and a stamped-addressed envelope provided to enable easy return of the questionnaire to the CTU.

8.3.2 14 Day Hospital Follow up

For all participants who are randomised and administered a second-line treatment in the ED, the '14 Day Follow Up' CRF should be completed 14 days after the second-line infusion was started.

The CRF should be completed using the recruiting sites' hospital records. If a recruited participant is transferred to another hospital, then follow up with the accepting hospital should be completed to ensure that the data recorded are accurate.

Organ failure at the 14 day follow up is classified as requiring specific organ support. This includes:

a) Cardiac failure requiring active cardiac support (inotropes etc.)
b) Renal failure requiring haemo- or peritoneal dialysis
c) Hepatic failure requiring specific hepatic support
d) Multi-organ failure (combination of a, b, c)
e) Stevens-Johnson syndrome or toxic epidermal necrolysis.

8.4 Blood Samples

Between 1.5mls - 2mls of blood will be taken between 1 and 2 hours following completion of the infusion in order to measure the blood levels of phenytoin and levetiracetam.

If participants were not recruited into this trial and administered phenytoin, as best current practise it would be expected that measurement of a blood level of phenytoin would still occur (28).

Analysis will only be undertaken for the provision of assays to determine serum concentration of the randomised treatment and any unused sample remaining upon completion of the assay will be destroyed.

8.4.1 Levetiracetam Sample Management

Blood levels of levetiracetam will be measured and analysed in an accredited central laboratory. Samples will be prepared and stored in the biochemistry department of each participating centre and will be sent to the central laboratory.

Samples should be processed and stored locally but should not be transferred to the central laboratory until after the participant has provided consent (see section 6.4). Should a potential participant, or their proxy where appropriate, decline consent the sample should be destroyed.

Results of these assays will not be communicated to clinical teams, but they may provide useful data to inform subsequent trials.

Instructions for collection of samples and transfer to the central laboratory are provided in a document supplementary to this protocol.

8.4.2 Phenytoin Sample Management

Analysis of phenytoin levels will be undertaken in the biochemistry department of the local centre and results provided to the clinical team. Blood levels of phenytoin will be measured as per routine clinical practice.

8.5 Consent Study

EcLiPSE will involve a mixed method study (Consent study) involving parents and EcLiPSE recruiters to explore approaches to recruitment and deferred consent. Led by Dr Kerry Woolfall (KW), the Consent study will examine: how information about the trial and deferred consent is exchanged during recruitment discussions; views on deferred consent; and the impact of an un-blinded trial design and potential treatment risks upon acceptability of deferred consent (29-31). The aim will be to identify recruitment and consent issues and potential solutions to inform EcLiPSE recruiter training materials. The Consent study will involve:

A. Routine audio-recording of EcLiPSE discussions (consultations) between families and trial recruiters;
B. Survey of parents/legal representatives after their EcLiPSE recruitment and consent discussion, survey conducted by completion of a questionnaire;
C. Telephone interviews with up to 25 parents (and 16-18 year old adults with capacity) who agree or decline deferred consent and one EcLiPSE trial recruiter (PI or research nurse) at participating sites;
D. Focus groups (6-10) including a training session with EcLiPSE trial recruiters at trial sites at the end of the first year.

The below table summaries when each section of the consent study is applicable per participant who was randomised to EcLiPSE and administered second-line treatment.

Table 2: Consent Study Applicability

Consent sought from	**Location consent was sought**	**Applicable sections of the consent study:**		
		A: Audio-recording	**B: Questionnaire**	**C: Interview**
Parent/legal representative	On-site	✓	✓	✓
Bereaved Parent/legal representative	On-site			✓
Adult with capacity	On-site	✓		✓
Parent/legal representative	Home		✓	✓
Bereaved Parent/legal representative	Home			✓
Adult with capacity	Home			✓

Note: Participants who were randomised but **not** administered second-line treatment will **not** be included in the consent study.

Parents can select which study elements (A, B or C, as applicable) they wish to take part in by ticking the relevant boxes on the EcLiPSE consent form.

8.5.1 Part A: Audio-recordings

Delegated EcLiPSE recruiters will routinely seek verbal permission to audio-record recruitment consultations when they first approach families about EcLiPSE on-site. If permission for audio-recording is declined by a family the recruitment consultation will not be recorded. If permission is given, the recruiter will activate an audio-recorder. If there is more than one trial discussion (e.g. an initial discussion followed by a full trial discussion after the family have considered the trial information) then all discussions should be recorded.

Completed audio-recordings will be uploaded to the 'Voicescript' website (http://www.voicescript.co.uk/file-manager/) for transcription. The 'Guidance for the management of audio recordings' should be used to ensure that the recordings are correctly stored and uploaded in accordance with the data protection act.

Audio-recording of trial consultations will take place for the first four months of the trial at each site, or until the sample target (data saturation point) is achieved. Sites will be informed when audio-recordings can stop.

Note: Refer to table 2 for audio-recordings applicability.

8.5.2 Part B: Parent/Legal Representative Questionnaires

At the end of the recruitment discussion EcLiPSE recruiters will ask all parents/legal representatives (including those who decline deferred consent) to complete the Consent Study Parent/Legal Representative Questionnaire, place it in a sealed stamped addressed envelope and return it to the recruiter to post to KW. A link to an online version is also provided at the top of the paper questionnaire to enable parents to complete the survey online if preferred (e.g. using their smartphones). Recruitment for questionnaires will take place throughout the trial.

In the rare instance that consent is not sought prior to discharge/transferred to another hospital, the questionnaire should be sent to parents/legal representatives along with the Parent/Legal representative information sheet and consent form to complete.

If consent has been given, but a questionnaire has not been received by the Consent Study team, a link to the questionnaire will be sent at the point at which an interview is arranged. However, no follow up will occur for any missing questionnaire by the Consent Study if consent has not been obtained for Consent Study follow up.

Note: Refer to table 2 for questionnaire applicability. In addition, if more than one parent/legal representative is involved in the consent discussion, then both are able to complete a questionnaire. By completing the questionnaire, this confirms that the parent/legal representative has consented to this providing this information.

8.5.3 Part C: Interviews

EcLiPSE recruiters will ask the adult/parent/legal representative to provide contact details on the EcLiPSE consent form if they wish to take part in a telephone interview. KW or a research assistant will make contact with families to arrange telephone interviews within one

month of consent. At this point parents who live in (or close to) the Merseyside area will be provided with the option of a face to face interview at their home if they prefer. Consent for EcLiPSE and receipt of the consent study questionnaire will be checked at this point. If questionnaires have not been received a link to the online questionnaire or postal copy including stamped addressed envelope will be sent prior to interview. All families who express an interest in taking part but are not selected for an interview will be contacted via telephone or email to thank them for their interest in the study.

All interviews will be conducted by KW or a research assistant who both have proven skills in the conduct of research in sensitive settings. Any distress during the interviews will be managed with care and compassion and participants will be free to decline to answer any questions that they do not wish to answer or to stop the interviews at any point. Any such families will be supported in obtaining appropriate help and, after discussion with the family, the lead clinician responsible for the child's care will be informed to offer any support.

8.5.4 Part D: Focus Groups

At the end of the first year email invitations will be used to invite EcLiPSE staff in 6-10 sites to take part in a focus group. Selection of sites for focus groups will be based upon accrual rates (high and low rates) and recruitment issues identified in the analysis of audio-recordings (A), questionnaires (B) and parent interviews (C). All focus groups and training will be facilitated by KW and a research assistant.

Throughout the trial KW will use findings from the Consent study to create short reports for EcLiPSE recruiters containing recommendations to assist approaches to recruitment and deferred consent.

8.6 Loss to Follow-up

Trial follow-up is by the trial RN until the time points specified in section 8.1. If any of the trial participants are lost to follow-up before the relevant time-point (e.g. lost due to transfer to another hospital), contact will initially be attempted through the trial RNs and the lead investigator at each centre.

8.7 Trial Closure

The end of the trial is defined to be the date of database lock. This is the date on which data modification privileges are withdrawn from the trial database.

9 STATISTICAL CONSIDERATIONS

A separate and full Statistical Analysis Plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed by the Trial Steering Committee (TSC). The main features of these planned statistical analyses are included here in the main protocol.

9.1 Method of Randomisation

The randomisation code list will be generated by a statistician (who is not involved with the EcLiPSE trial) at the CTU. Participants will be randomised to levetiracetam or phenytoin in a ratio of 1:1. Randomisation will be stratified by centre. Sequentially numbered randomisation packs will be provided for each ED.

9.2 Outcome Measures

The primary and secondary outcomes, as well as the precise definitions of the outcomes that are provided in section 4.

9.3 Sample Size Estimation

The primary outcome is time to cessation of all visible signs of convulsive seizure activity measured from the point of randomisation. Phenytoin has a reported successful seizure cessation rate of 50-60% (7). Successful seizure-cessation has been reported to be 76-100% (8-17). When the sample size in each group is 140 participants, with a total number of events of 183, a 0.05 level two-sided log- rank test for equality of survival curves will have 80% power to detect an increase in seizure cessation from 60% to 75%, (a constant hazard ratio of 0.661). A total of 308 participants will allow for 10% loss to follow up.

Due to deferred consent process this will require 308 randomised patients for whom consent has been sought and randomised treatment received.

9.4 Interim Monitoring and Analyses

The trial will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) who will assess the trial data and take into account the current world-wide evidence. The IDSMC members will comply with a trial-specific IDSMC charter according to International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

The trial statistician at the CTU will prepare the report for the IDSMC, the contents of which will be agreed by the IDSMC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further participants or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 17) as to the continuation of the trial.

9.5 Analysis Plan

The primary analysis will use the intention to treat principle. A 5% level of statistical significance will be used throughout and all results will be presented with 95% confidence intervals. The primary outcome is a time to event outcome and will be analysed using the log-rank test and Kaplan-Meier curves. Dichotomous outcomes will be analysed using the chi- square test and presented with relative risks. Adjusted analyses will be conducted using Cox Proportional Hazards models or logistic regression as appropriate. Variables to be included in the models will be determined from known prognostic factors. Adverse events will be presented using descriptive statistics. No formal statistical tests will be used to compare randomised groups for baseline characteristics or adverse events. Reasons for missing data will be monitored and collected. Levels of missing data are expected to be low. Rates and reasons for not obtaining deferred consent will be monitored throughout the study. The Haybittle-Peto approach will be employed for interim analyses with 99.9% confidence intervals but importantly decisions around trial continuation will not be based on p-values alone.

9.6 Consent Study Analyses

Analysis of data from the mixed method Consent Study will be assisted using NVivo 8 qualitative data analysis package and SPSS software for statistical analysis. Quantitative analysis will involve simple descriptive statistics and the chi-square test for trend. Qualitative data from will be analysed thematically (32). Data from study methods (A, B, C, D) will be analysed separately then synthesised (33) through the use of constant comparative analysis (34).

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

10.1.1 Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

10.1.2 Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

10.1.3 Unexpected Adverse Reaction (UAR)

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- In the case of a product with a marketing authorization, in the summary of product characteristics for that product.

10.1.4 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

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

10.2.2 Do Not Include

- Prolongation of hospital stay due to social factors, for example, geographical location of the participant's home
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms (see 10.8.4)
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.

10.3 Notes on AE Recording Timelines

All adverse events occurring from randomisation until 24 hours after the second-line treatment infusion had started should be recorded and reported.

It is not expected that any Adverse Reactions would be observed 24 hours after the second-line treatment infusion had started, but the local investigator should report any adverse events that they feel are related to the study medication, regardless of the timing.

If death or organ failure is noted at the 14 day safety follow up this should be recorded on the '14 day follow up' CRF, however, no additional reporting is required unless the local investigator feels that the event(s) are related to the study medication.

For patients who are randomised but not administered second-line treatment, adverse events do not need to be recorded and reported.

10.4 Notes on Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.5 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 3.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others regarding a SUSAR, the MHRA will be informed of both points of view.

Table 3: Definitions of Causality

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

10.6 Expectedness

It is not a regulatory requirement for a reporting physician to provide their opinion of expectedness. Therefore, the reporting physician at the research site will not be asked to make the assessment of expectedness. The assessment of expectedness will be made by the CI (or designated other) using the reference SmPCs for EcLiPSE following receipt of the SAE form at CTU.

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.

All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as **serious** and **unexpected** by the CI (see section 10.2 and SmPC for list of Expected Adverse Events) will be reported as a SUSAR.

10.7 Follow-up after Adverse Events

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

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

See 10.8.4 for follow up of pregnancies.

10.8 Reporting Procedures

All adverse events should be reported as detailed in section 10.3. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTU in the first instance. A flowchart is given below to aid in determining reporting requirements.

10.8.1 Non-serious ARs/AEs

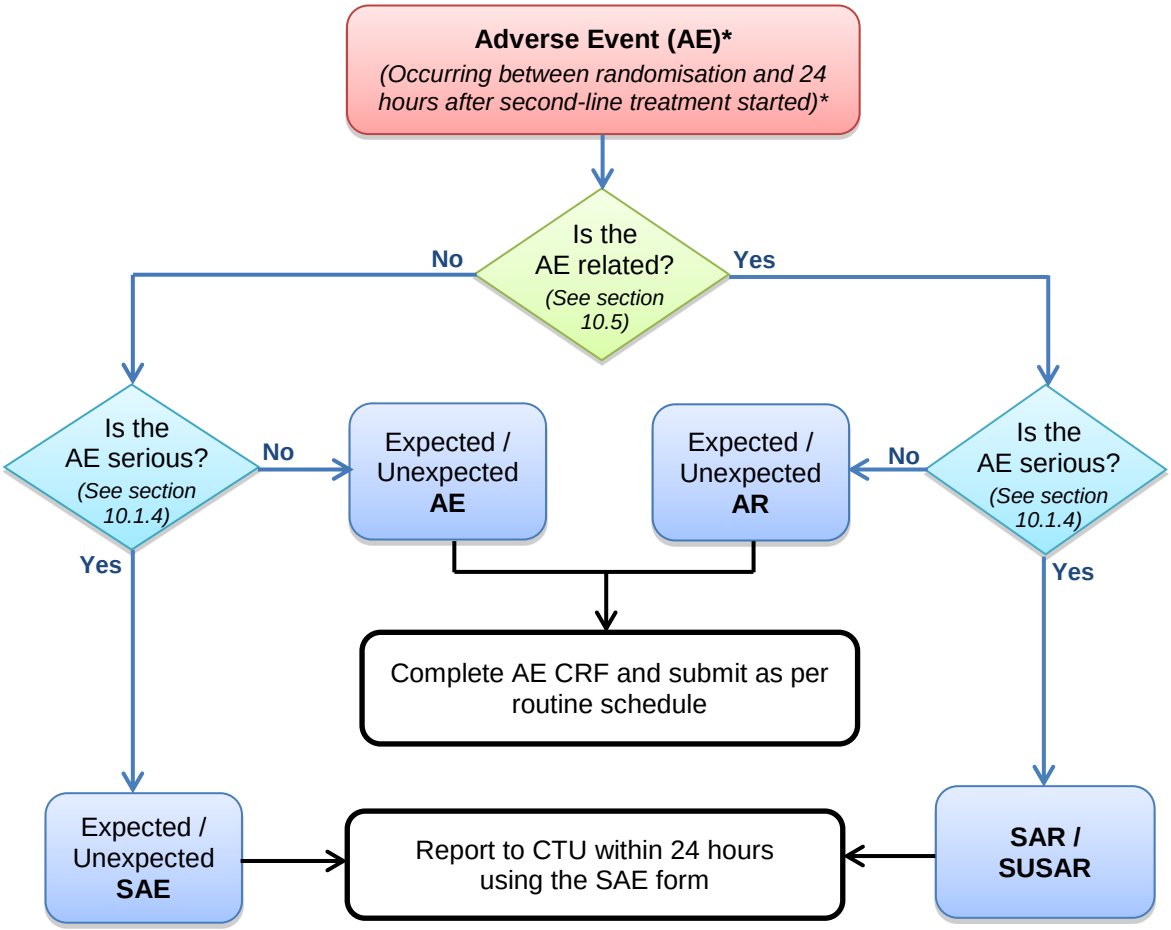
All such events, whether expected or not, should be recorded on an Adverse Event Form, which should be transmitted to the CTU within seven days of the participant completing the trial.

10.8.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The CTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators and members of the IDSMC and TSC will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required locally.

10.8.3 Flowchart for Reporting Requirements of Adverse Events



**If an adverse event occurs outside of this time window and the local investigator feels that the event is related to the second-line treatment administered, the above process should still be followed.*

10.8.4 Reporting of Pregnancy

The likelihood of pregnancy in the EcLiPSE study population is very low. This is because of the age (<18 years) and characteristics (chronic epilepsy with or without co-morbid problems including learning difficulties, cerebral palsy and autistic spectrum disorder) of the patient population.

Due to the emergency nature of the trial interventions it will not be possible to establish pregnancy status prior to randomisation if this is not already known. As is usual clinical practice in such emergency situations, treatment will not be delayed in order to undertake a pregnancy test.

If it is discovered that the participant was pregnant during treatment, this should be reported to the coordinating centre using a pregnancy CRF within 24 hours of awareness and the pregnancy followed up until after the outcome using the pregnancy CRF.

The investigator should contact the participant to discuss the risks of continuing with the pregnancy and the possible effect to the foetus. Appropriate Obstetric care should be arranged.

Pregnancies must be reported by faxing a completed pregnancy form within 24 hours of the site becoming aware of the event to the CTU

Fax: 0151 282 4721

10.8.5 Reporting of Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any study drug overdose (classified in this study as above 20% of the recommended dose) or incorrect administration of study drug should be noted on the CRF. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE CRF. If the associated AE fulfils the serious criteria, the event should be reported to the CTU immediately (i.e., no more than 24 hours after learning of the event).

10.8.6 Reporting of Death

All deaths that occur during the protocol-specified AE reporting period regardless of relationship to study drug, must be recorded. All deaths should be reported on a Serious Adverse Event CRF and faxed to the CTU within 24 hours.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE CRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Serious Adverse Event CRF. If the cause of death subsequently becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

10.9 Investigator Responsibilities

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the CTU on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Participant number
- A description of the event
- Date of onset
- Current status
- Study treatment
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Reporting Investigator Authorisation

i. The SAE form should be completed by a designated investigator, a physician named on the 'Delegation of authority and signature log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the CTU. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTU. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE to the CTU research sites should also telephone the appropriate trial co-ordinator/data manager on telephone number **0151 282 4722** to advise that an SAE report has been submitted.

iii. Send the SAE form by fax (within 24 hours or next working day) to the CTU:

Fax Number: 0151 282 4721

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vii. The participant **must** be identified by trial number, date of birth and initials only. The participant's name **should not** be used on any correspondence.

10.10 Contact Details and Out-of-hours Medical Cover

EcLiPSE is being conducted within EDs of centres with expertise in the management of paediatric emergencies. Duration of participation for individuals is 24 hours after the second-line treatment infusion had started with an additional questionnaire and safety follow up at 14 days. Clinical teams responsible for the care of patients beyond the ED will be aware of randomisation and treatment administered, enabling them to make appropriate and informed decisions about their care in the event of an emergency. As such, emergency clinical care out of hours will be provided as local standard of care.

All patients will be issued with a copy of the signed information sheet and consent form, which they will be instructed to carry with them for the next 24 hours. This document will include information about the patient's participation in the EcLiPSE trial and contacts in the research team locally who may be contacted if needed. During office hours Doctors Appleton, Iyer, Shrouk and Lyttle will provide medical advice in relation to children recruited to EcLiPSE. They can be contacted via the EcLiPSE trial coordinator at the CTU:

Tel: 00 44 (0) 151 282 4722
Fax: 00 44 (0) 151 282 4721
E-mail: eclipse@liverpool.ac.uk

11 ETHICAL CONSIDERATIONS

11.1 Ethical Issues

The specific ethical issues are:

A. Informed consent in a paediatric emergency care setting

Prospective informed consent cannot be sought for EcLiPSE as:

- seizures are a medical emergency and there is insufficient time to obtain informed consent within the therapeutic window (second-line anticonvulsant agents should ideally be given within 5-15 minutes of arrival in ED);
- staff priorities are assessment and management of airway, breathing, circulation with establishment of IV access and brief pertinent clinical history;
- parents may not be present; and even when parents are present seizures are very distressing, compromising parents' capacity to make an informed decision and provide consent.

In 2008, the UK amended its regulations to allow deferred consent in paediatric emergency trials that fulfil specific criteria. This trial will comply with these regulations as the emergency need for immediate treatment will not allow informed consent prior to randomisation. Deferred consent will be sought as soon as is practicably possible (within 24 hours). The planned procedure (see sections 6.2, 6.3 and section 6.4 for the recruitment, randomisation and consent processes) had been developed by the project team using findings from co-applicant Dr Kerry Woolfall's (KWs) research with parents, which has explored the use and acceptability of deferred consent in EcLiPSE and other emergency care trials. KW will lead the Consent study to explore the experiences of parents and practitioners involved in EcLiPSE. Refer to section 8.5 for further details.

B. Assent from critically ill patients (minors)

Due to the physical status of the target population it may not be possible to involve children in the consenting process. The ethics application will be supported by parent and child information sheets and parent and child consent/assent forms (see list of consent/assent forms in section 6.4). Deferred assent of children and young people will be obtained if their condition allows.

C. Recruitment of adults lacking capacity

Due to the physical status of the target population it may not be possible to involve eligible adults in the consenting process. Additionally, most, if not all of the adult participants (16-18 years) are likely to have severe and drug-resistant epilepsy and additional co-morbid problems, including moderate or severe learning difficulties and autistic spectrum disorder and therefore may not have the capacity to give informed consent outside of the acute emergency setting. It is likely that less than 2% of all participants will be aged between 16 and 18 years.

EcLiPSE fulfils the criteria set out in UK law to allow adults not able to consent for themselves to be recruited into Clinical Trials of Investigational Medicinal Products (CTIMPs) without prior consent in emergency situations. In these situations deferred consent from the

trial participant will be sought should they have capacity to do so. However for adults lacking capacity a legal representative will be sought. The legal representative will be asked to provide consent on behalf of an adult lacking capacity to provide consent themselves. The informed consent given by the legal representative shall represent the presumed will of the incapacitated adult. See section 6.4.7 for definitions of legal representatives.

If it is appropriate the participants themselves will also receive information, according to their capacity of understanding, about the trial and its risks and benefits.

11.2 Ethical Approval

The trial protocol, including the Parent/Patient Information Sheets and Consent/Assent forms and all other relevant trial documentation will be submitted for review by the Research Ethics Committee (REC). All participating centres must be granted NHS permission prior to commencing recruitment. A copy of localised versions of the Parent/Patient Information and Consent/Assent form should be forwarded to CTU before the centre is initiated and patients recruited.

12 REGULATORY APPROVAL

This trial falls within the remit of the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial has been registered on EudraCT. The EudraCT reference is 2014-002188-13.

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A detailed risk assessment is performed for each trial coordinated by the CTU to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial and are described in the Trial Monitoring Plan. Monitoring can take the form of on-site visits or central monitoring

Details of the monitoring to be carried out for the EcLiPSE study are included in the EcLiPSE Trial Monitoring Plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 17.

14 RISK ASSESSMENT

In accordance with the CTRC SOP TM005 the trial risk assessment is completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- CTRC Director

In conducting this risk assessment, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A *'no higher than that of standard medical care';*
Type B *'somewhat higher than that of standard medical care';*
Type C *'markedly higher than that of standard medical care'.*

Intravenous levetiracetam has been shown to be safe and effective in treating adults and children with convulsive and non-convulsive status epilepticus and with acute repetitive seizures (8-17). Its success rate varies between 76 and 100% (8-17). A recently published randomised study of the initial intravenous treatment of convulsive status epilepticus in adults reported seizure cessation rates of 76.3% (16). Although EcLiPSE will use IV levetiracetam outside the manufacturer's indication, the IMP in the EcLiPSE trial is categorised as Type A *'no higher than that of standard medical care'*. This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

14.1 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*

Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the case report form (CRF) and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. EcLiPSE Source document lists will be produced for each site prior to trial initiation.

The CRF will be considered the source document for data where no prior record exists and which is recorded directly in the CRF.

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

14.2 Data Capture Methods

14.2.1 Case Report Forms

Sites will be issued with sequentially numbered randomisation packs to be opened upon presentation of an eligible patient. The packs will each contain the case report form to be completed whilst the patient is in the ED. The other CRFs will be provided separately, to be completed as soon as is feasible according to schedule.

CRFs should be completed and sent to the CTU within 7 days of the scheduled assessment, unless stated otherwise. Copies of completed CRFs must be retained at site in the site file.

14.2.2 Central Monitoring

Data stored at CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation of authority and signature log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the EcLiPSE trial monitoring plan.

14.3 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, etc. Since this affects the patient's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form. Clinical site monitoring will be detailed in the EcLiPSE trial monitoring plan.

14.3.1 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Case report forms will be labelled with the randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The CTU will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the CTU by recruiting centres, which requires that name data will be transferred to the CTU.

This transfer of identifiable data is disclosed in the PISC. The CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

14.3.2 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, site visits will be conducted and source verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The minimum key staff required to be recorded on the delegation of authority and signature log in order for the site to be eligible to be initiated will be determined by TMG;
- The PI and other key staff from each centre will attend site initiation training, coordinated by the CTU, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol;
- The Trial Coordinator at the CTU will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;
- The Trial Management Group is to monitor screening, randomisation and consent rates between centres;
- Data quality checks will be undertaken in line with the EcLiPSE Data Management Plan;
- Independent oversight of the trial will be provided by the Independent Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

The Sponsor may undertake a number of site audits at selected trial sites throughout the trial.

14.4 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTU undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTU will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 INDEMNITY

EcLiPSE is co-sponsored by the University of Liverpool and Alder Hey Children's NHS Foundation Trust and co-ordinated by the MC CTU, part of the CTRC, in the University of Liverpool.

The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

16 FINANCIAL ARRANGEMENTS

This trial is funded by the NIHR Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating centres that will describe financial arrangements.

16.1 NHS Research Costs

16.1.1 Per Site

To reflect site personnel time to fulfil the needs of the research e.g. preparing for an attending initiation/ monitoring meetings, a per site payment is included in the budget and detailed in contracts.

16.1.2 Per Patient Recruited Payment

Research related activity, including data collection, will be supported by a *per patient* payment. In EcLiPSE the patient care pathway mirrors usual care in this acute emergency situation and data collection forms will be formatted to ensure that critical variables can be collected in the busy emergency setting. However in order to support the robust recruitment and follow-up of participants a per patient payment is budgeted and detailed in contracts.

16.2 NHS Support Costs

Research related activity, including data collection, will be supported by a *per patient* payment described above. Other patient care related activities are in line with usual care and therefore additional service support for staff time is not requested. This trial will be entered into the NIHR CRN portfolio as part of the paediatric speciality and infrastructure support will be available through the CRN network.

16.3 Treatment Costs

Supplies for the trial will be secured though the usual NHS commissioning arrangements and treatment costs are covered via usual NHS arrangements.

17 TRIAL COMMITTEES

17.1 Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running and management of the trial and will meet frequently during set-up and the pilot, reducing frequency as the trial progresses (at least 3 times per year). **Refer to the TMG terms of reference and trial oversight committee membership document for further details**.

17.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. **Refer to the TSC terms of reference and trial oversight committee membership document for further details.**

17.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually).

The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study. **Refer to the IDSMC charter and trial oversight committee membership document for further details.**

18 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

19 PROTOCOL AMENDMENTS

19.1 Version 1.0 (13/01/2015)

Original Approved version.

19.2 Version 2.0 (23/04/2015)

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
1	Protocol summary	• Study participation increased from 24 hours to 14 days. Follow up at 14 days for safety only. • Schematic of study design: updated to align with new follow up and change to inclusion criteria number 3.
4.1	Primary endpoint	• Defined as: Time to cessation of all visible signs of convulsive seizure activity *will be calculated from the time of randomisation. A secondary analysis will use time from the start of the infusion.*
4.3	Internal pilot	• Clarified that the internal pilot will involve 5 centres – but other centres may also open during this period.
5.1	Inclusion criteria	• Inclusion criteria 2: Definitions of presenting seizures have been clarified. • Inclusion criteria 3: Amended to '*First-line treatment* administered *according to APLS guidelines or the child's personalised rescue care plan* in order to try and terminate the *presenting* seizure' • Eligibility notes: Amended to align with the changes to the inclusion criteria and clarify the definitions of first-line treatment.
5.2	Exclusion criteria	• Exclusion criteria 3: Amended to align with updated inclusion criteria 3. • Exclusion criteria 6: Amended to 'Known to have previously been *treated as part of EcLiPSE*'
6.1	Screening	• Process for assessing eligibility clarified. • Screening will now commence once a child has arrived in the ED and has started first-line treatment. Reference to two doses of benzodiazepines removed.
6.3	Randomisation	• Change to randomisation envelopes used. Randomisation packs will instead include CRFs that are prepopulated with the randomisation number and treatment allocation. • Process for patients who are randomised but not treated with second-line treatment whilst in the ED defined.
6.4.11	Patients randomised but not treated with second-line treatment in the ED	• Process for obtaining consent for patients randomised but not administered second-line treatment defined.
7.1	Trial treatments introduction	• Guidance on 'actual' weight removed.
7.3.2	Preparation, Dosage and Administration of Levetiracetam	• Following sentence removed to ensure clarity on the dilution of levetiracetam *'Levetiracetam should be diluted in accordance with the manufacturers SmPC'*.

7.6	Accountability procedures for study treatments	• Updated to align with new randomisation packs (see section 6.3).
7.7	Assessment of compliance with study treatments	• Updated to align with new randomisation packs (see section 6.3).
7.10	Co-enrolment guidelines	• Updated to include *'should co-enrolment issues arise, patients are permitted to enter EcLiPSE whilst participating in another trial. This is providing that the other trial will not impact the EcLiPSE primary endpoint. Any queries regarding co-enrolment should be discussed with the CTU who will contact the Chief Investigator'.*
8.1	Schedule for follow up	• New follow up period defined to include: o follow up for patients not administered second-line treatment o 14 day safety follow up
Table 1	Trial assessments	• Follow up time points clarified. • Height assessment removed. • Heart rate, oxygen saturation, respiratory rate and blood pressure assessment removed. • 14 day safety follow-up added.
8.2.1	Seizure activity	• Seizure follow up clarified as for '*24 hours after the second-line infusion was started'*.
8.3	Procedures for assessing safety	• Clarified adverse events to be recorded from randomisation until 24 hours after second-line infusion started. • Process for 14 day safety follow up added: o 14 day follow up questionnaire o 14 day hospital follow up
8.4	Blood samples	• Blood sample to be taken updated to '*between 1.5mls – 2mls'*
8.5	Consent study	• Table inserted to clarify when each section of the consent study is applicable.
8.5.1	Part A: Audio-recordings	• Transcriptions to be completed by 'Voicescript' website
9.3	Sample size estimate	• Updated to include *'Due to deferred consent process this will require 308 randomised patients for whom consent has been sought and randomised treatment received.'*
10.3	Notes on AE recording timelines	• Updated to align with changes to follow up as per section 8.3.
10.8.3	Flowchart for reporting requirements of adverse events	• Updated to align with changes to follow up as per section 8.3.
10.8.5	Reporting of overdose	• Overdose classified as above 20% of the recommended dose.
14.2.1	Case report forms	• Updated as per new randomisation process. • Reference to two part no carbon copy removed.
N/A	N/A	• Other minor typographical errors corrections and clarifications in order to ensure consistency made throughout.

19.3 Version 3.0 (17/06/2015)

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
7.1	Trial Treatments Introduction	• Concentration of levetiracetam updated to: **A maximum of** 50mg/ml with sodium chloride 0.9%. • Concentration of phenytoin updated to: **A maximum of** 10mg/ml with sodium chloride 0.9%.
7.3.2	Preparation, Dosage and Administration of Levetiracetam	• Concentration of levetiracetam updated to: **A maximum of** 50mg/ml with sodium chloride 0.9%.
7.4.2	Preparation, Dosage and Administration of Phenytoin	• Concentration of phenytoin updated to: **A maximum of** 10mg/ml with sodium chloride 0.9%.

19.4 Version 4.0 (27/08/2015)

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Front page	N/A	• Additional reference numbers inserted
1	Protocol summary: Schematic study design	• Maximum dose and infusion times for phenytoin updated.
7.1	Trial Treatments Introduction	• Maximum dose of phenytoin increased to 2000mg. • Infusion times for phenytoin updated: - Infusion time for dose ≤1000mg: over 20 minutes - Infusion time for dose >1000mg and ≤1500mg: Between 20 – 30 minutes - Infusion time for dose >1500mg and ≤2000mg: Between 30 – 40 minutes.
7.3.2	Preparation, Dosage and Administration of Levetiracetam	• Reference to the New Zealand guidelines updated
7.4.2	Preparation, Dosage and Administration of Phenytoin	• Updated to confirm that the *'total maximum dose of phenytoin administered should be 2000mg. However, sites should confirm prior to study start if their local procedure states that the maximum phenytoin dose is less than 2000mg. If this is the case then maximum dose for phenytoin should be as per local procedure and should be adhered to.'* • Infusion times for phenytoin updated.

8.5.2	Part B: Parent/Legal Representative Questionnaires	• Updated to confirm online version of the questionnaire can be completed. • Clarified that if more than one parent/legal representative is involved in the consent discussion, both can complete a questionnaire. • Updated to confirm that the Consent Study team may follow up for missing questionnaires when completing consent follow up, if consent has been obtained for this.
8.5.3	Part C: Interviews	• Updated to allow face-to-face interviews for parents/legal representatives who live in (or close to) the Merseyside area if this preferred.
N/A	N/A	• Other minor typographical errors corrections and clarifications in order to ensure consistency made throughout.

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21 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol that are separately maintained and version controlled are listed in the 'EcLiPSE Documents Supplementary to protocol' log. Any of the supplementary documents subject to ethical review are submitted as separate version controlled documents.