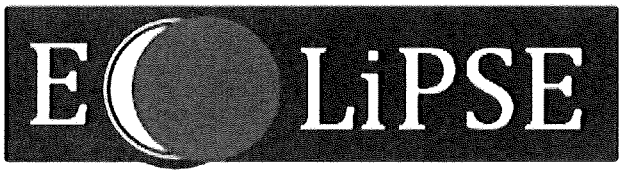

Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE) – an open label randomised controlled Trial

EudraCT number: 2014-002188-13

ISRCTN: 22567894

Statistical Analysis Plan: Final Analysis version 2.0 15/05/2018

	ORIGINATED BY	APPROVED BY
Name	Ashley Best	Carrol Gamble
Title	Trial Statistician	Senior Statistician
Date	15/05/2018	
Protocol Version and Date	Version 5.0 05/04/2017	

1. Change Control

Protocol version	Updated SAP version no.	Section number changed	Description of change	Reason for change	Date changed
V5.0	V2.0	2	Added space for independent statistician signature	To allow independent statistician to approve changes made to SAP following blind review	15/05/18
V5.0	V2.0	5	Updated protocol date and version number	To ensure correct version	15/05/18
V5.0	V2.0	6	"Guidelines" capitalised and "adverse" inserted before "side effects"	Clarification added	15/05/18
V5.0	V2.0	8.3	Removed dose as a reason for varying length of infusion time	Corrected from V1.0. Dose does not impact infusion time.	15/05/18
V5.0	V2.0	8.3	"Length" changed to "duration"	Clarification added	15/05/18
V5.0	V2.0	8.4	Removed number of participants	Covered in section 10	15/05/18
V5.0	V2.0	8.4	Removed details of randomisation pack	Not relevant to details of blinding	15/05/18
V5.0	V2.0	8.7	Grammar and typographical errors corrected	n/a	15/05/18
V5.0	V2.0	8.8	Grammar and typographical errors corrected. Added that the consent letter is received by the CTRC	Clarification added	15/05/18
V5.0	V2.0	10	Added details of the required sample size	Moved from section 8.4	15/05/18
V5.0	V2.0	12	Added details of number of decimal places to be reported	Clarification added	15/05/18
V5.0	V2.0	14.1	Number of participants who declined consent will be reported overall in the flow diagram	The numbers declining consent is known but it is not known if they were treated or not treated.	15/05/18
V5.0	V2.0	14.1	Removed inverse of the details to be presented in the table.	To avoid duplication of information	15/05/18
V5.0	V2.0	14.1	Added details for the total number of participants who declined consent which will be included in the screening summary table	Clarification added	15/05/18
V5.0	V2.0	14.1	Clarification added to number of treated participants that this will be presented by arm and overall	Clarification added	15/05/18
V5.0	V2.0	15	Removed selected details of some of the listed possible protocol deviations and highlighted	Clarification added	15/05/18

			where Data Monitoring Plan can be found.		
V5.0	V2.0	17.1	Added that allocations were random.	Clarification added	15/05/18
V5.0	V2.0	17.1	Removed statement that imputations will not be made	Imputations will be made as described in other sections	15/05/18
V5.0	V2.0	17.2	Added that baseline data will only be presented for treated patients	Documented in internal meeting minutes dated 08/05/2018	15/05/18
V5.0	V2.0	17.2	Updated how age and weight will be presented (Skewed data therefore median and IQR presented)	Recommended following blinded review of data by an independent statistician	15/05/18
V5.0	V2.0	17.2	Baseline characteristic changed from "whether it's their first seizure (yes/no)" to "whether the index episode of CSE is their it's their first seizure (yes/no)	Clarification added	15/05/18
V5.0	V2.0	17.3	Typographical error correction	n/a	15/05/18
V5.0	V2.0	17.4.1.1	Updated the derivation of primary outcome to reflect that an RSI is not an event but is censored at time plus 12 hours rather than 24 hours.	This decision was made following recommendations and agreement of the TSC. TSC document attached as an appendix.	15/05/18
V5.0	V2.0	17.4.1.2	Age was removed from the logistic regression model	Recommended following blinded review of data by an independent statistician due to correlation with weight.	15/05/18
V5.0	V2.0	17.4.1.2	Removed details of further analysis to be conducted if proportional hazards assumption is invalidated.	See (Campbell 2014), for details.	15/05/18
V5.0	V2.0	17.4.1.3	Added section and moved the details of imputations to be made for primary outcome.	Moved from section 18	15/05/18
V5.0	V2.0	17.4.1.3	Added that participants with a missing end of infusion time will be imputed based on median time of infusion for each treatment group.	Recommended following blinded review of data by an independent statistician	15/05/18
V5.0	V2.0	17.4.1.3	Added that participants with a missing seizure cessation time whose seizure is known to have stopped will be classed as event with imputations made based on median	Recommended following blinded review of data by an independent statistician	15/05/18

			time to seizure end time for each treatment group.		
V5.0	V2.0	17.4.2.2	Age was removed from the logistic regression model	Recommended following blinded review of data by an independent statistician due to correlation with weight.	15/05/18
V5.0	V2.0	17.4.2.2	Typographical error correction	n/a	15/05/18
V5.0	V2.0	17.4.5.1	Inserted that the study drug assessment of causality is made by the Chief Investigator	Clarification added	15/05/18
V5.0	V2.0	17.4.5.2	Removed planned analysis of SARs	Recommended following blinded review of data by an independent statistician due to lack of events	15/05/18
V5.0	V2.0	19	Added subheadings to each of the additional analyses.	Clarification added	15/05/18
V5.0	V2.0	19	Added reasoning to how the robustness of planned sensitivity analysis will be evaluated	Clarification added	15/05/18
V5.0	V2.0	19.3	The planned sensitivity analysis was given more detail as to when patients where censored (at the point of 2nd second-line treatment being administered)	Clarification added	15/05/18
V5.0	V2.0	19.4	Added section regarding additional competing risks analysis to be conducted	Recommended by the TSC	15/05/18
V5.0	V2.0	19.5	Added a sensitivity analysis to consider the effect of imputations made for primary outcome analysis	Recommended following blinded review of data by an independent statistician	15/05/18

2. Approval and agreement

At a minimum two versions of the SAP should be approved and stored within the statistics trial file.

1. SAP version 1.0 should be created after it has been reviewed and signed-off to ensure all are in agreement with the planned analysis and no further changes are foreseen.

2. The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: 2.0

Trial Statistician

Name NAOMI BACON

Signed N.Bacon Date 15/05/2018

Senior Statistician

Name CARROL GAMBLE

Signed [signature] Date 15/05/2018

Chief Investigator/clinical lead

Name RICHARD APPLETON

Signed [signature] Date 15.05.2018

Independent statistician undertaking blind review

Name Ashley Jones

Signed [signature] Date 15/5/18

3. Roles and responsibilities

N Bacon (Department of Biostatistics, University of Liverpool): Trial Statistician, C Gamble (Department of Biostatistics, University of Liverpool): Senior Statistician, R Appleton (Alder Hey Children's NHS Foundation Trust): Chief Investigator.

Author's contributions

N Bacon and C Gamble proposed the statistical analysis plan. N Bacon drafted the manuscript. C Gamble and R Appleton read, amended and approved the statistical analysis plan. A Best updated the SAP from V1.0 to V2.0 as a blinded statistician following comments from the TSC and blind review by independent statistician and Chief Investigator.

4. List of abbreviations and definitions of terms

AE	Adverse Event
APLS	Advanced Paediatric Life Support
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
CSE	Convulsive Status Epilepticus
EcLiPSE	Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children
ED	Emergency Department
GP	General Practitioner
IDSMC	Independent Data and Safety Monitoring Committee
IQR	Inter-quartile Range
ITT	Intention to Treat
IV	Intravenous
RSI	Rapid Sequence Intubation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOP	Standard Operating Procedure

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5. Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned **final** analyses for the study "Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE)". The planned statistical analyses described within this document are compliant with those specified in brief within the EcLiPSE protocol version 5.0 dated 05/04/2017.

This study is 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, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) 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.

These planned analyses will be performed by the trial statistician.

This study is a clinical trial of a medicinal product and is registered on the EudraCT database. The SAP has been developed to support the posting of results on the EudraCT system. This is a regulatory requirement which should be fulfilled within 6 months after the end of the study as defined within the clinical trial protocol.

The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS version 9.3 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and standard operating procedure (SOP) TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001: Statistical Analysis and Reporting.

6. Background and Rationale

The rationale for the trial is outlined in the protocol. To be brief, the management for children admitted to the Emergency Department (ED) who present with Convulsive Status Epilepticus (CSE) follows the Advanced Paediatric Life Support (APLS) guidelines. The APLS Guideline use phenytoin as the first-choice second-line 'standard' anticonvulsant and is administered if the child's seizure has not responded to two doses of a benzodiazepine. Levetiracetam is an anticonvulsant which is used for long term maintenance in its oral form. There is some evidence that when used intravenously it can be an alternative second-line treatment in the emergency setting and it is believed that levetiracetam has fewer adverse side effects than phenytoin. A definitive randomised trial is needed to compare levetiracetam against the standard treatment of phenytoin for stopping seizures.

7. EcLiPSE Study Objectives

The objective of this trial is to determine the effectiveness of intravenous (IV) levetiracetam compared to intravenous phenytoin as second-line anticonvulsant for the emergency management of CSE in children.

The null hypothesis is that there is no difference in time to cessation of all visible signs of convulsive seizure activity between the intervention (levetiracetam) group and the control (phenytoin) group. The alternative hypothesis is that there is a difference between the two groups.

The secondary objective is to determine the safety of intravenous (IV) levetiracetam compared to intravenous phenytoin as second-line anticonvulsant for the emergency management of CSE in children.

The null hypothesis is that there is no difference in safety between the intervention (levetiracetam) group and the control (phenytoin) group. The alternative hypothesis is that there is a difference between the two groups.

8. Investigational Plan and Study Design

8.1 Overall study design and plan- description

EcLiPSE is a two-arm, multi-centre, superiority, open label randomised controlled trial. Treatment allocation is a 1:1 ratio. Patients who present with CSE in the ED are randomised to either phenytoin or levetiracetam. EcLiPSE uses deferred consent (details can be found in section 6.4 of the protocol). A sub-study (Consent study) exploring approaches to recruitment and deferred consent is being undertaken alongside EcLiPSE. Details of the Consent study can be found in section 8.5 of the protocol. It should be noted that this SAP only relates to the main EcLiPSE trial and not the Consent study.

The trial included an 18 month internal pilot. Full details of the success criteria can be found in section 9.3 of the protocol. If the internal pilot determined continuation was not feasible then this analysis plan will be applied to the data collected.

8.2 Treatments studied

The two active drugs used in EcLiPSE are levetiracetam and phenytoin:

- Levetiracetam
- Phenytoin

Dosing and administration details can be found in section 7 of the study protocol. Whether additional anticonvulsants were given alongside the second line treatment (such as paraldehyde) will be recorded on the CRF "Form 1: Randomisation & Second Line Treatment".

8.3 Treatment compliance

Both treatments are delivered as a single infusion once the patient has been randomised to EcLiPSE. The duration of infusion time varies by drug (see section 7 of the protocol for details). It should be noted in the patient's medical notes and the CRF "Form 1: Randomisation & Second Line Treatment" if the full infusion and dose has been given.

Possible reasons for non-compliance are:

- Infusion was not completed.
- Dose given was too high.

- Infusion duration was too long.
- Infusion duration was too short.
- Patient randomised but not treated (most likely due to seizure stopping).
- Patient given other treatment to that randomised.
- Infusion via interosseous rather than intravenous route.

The reasons for infusion not completed or exceeded expected duration of infusion time will be recorded on the CRF "Form 1: Randomisation & Second Line Treatment". Reasons include "Extravasation at infusion site requiring re-siting of IV access" or "Other (specified)".

8.4 Patient population studied

Males and females aged 6 months to 18 years, who present with CSE that fails to respond to first-line treatment will be entered into EcLiPSE. 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.

8.5 Inclusion criteria

The inclusion criteria can be found in section 5 of the protocol.

8.6 Exclusion criteria

The exclusion criteria can be found in section 5 of the protocol.

8.7 Removal of patients from therapy or assessment

There are 10 minutes between giving the second dose of benzodiazepine and starting the randomised treatment infusion. In routine clinical practice the nursing staff would be preparing the randomised infusion so it is ready to administer immediately if the child is still seizing at the end of those 10 minutes. As the nursing staff requires time to prepare the infusion, the randomisation envelopes will be opened in advance of the decision to treat in order to know which drug to start preparing. However if the child stops seizing during these 10 minutes, and does not restart prior to leaving the ED, then they will not receive the infusion but will still have been randomised. In this situation, for those patients who were randomised but no second-line anticonvulsant(s) was(were) given, only information up to section 5 on CRF "Form 1:

Randomisation & Second Line Treatment" will be expected to be completed. These patients will be excluded from primary and secondary analyses.

8.8 Consent process

EcLiPSE uses deferred consent (details can be found in section 6.4 of the protocol). Consent is sought after randomisation and the child has stopped seizing.

For randomised patients for whom consent has not been sought prior to discharge, EcLiPSE uses an opt-out procedure. Therefore if a patient was randomised, and not approached during hospital stay for consent (and are alive) they will be contacted via phone in the first instance and then via post. If they do not respond to this letter, their data will be included in the analyses. If a patient is missed while in hospital and has died, they will be sent a consent form via post to return to the CTRC. If the parents/legal representatives do not respond to this letter then one further letter will be sent. If no response to this letter is received by the CTRC, their data will be included in the analyses.

8.9 Blinding

EcLiPSE is an open label trial and the investigators and patients (and parents/legal representatives) will not be blind to allocated treatment.

8.10 Method of assignment to treatment

Full details of the randomisation procedure can be found in sections 6.3 and 9.1 of the protocol. The randomisation lists were generated by a statistician (who is not involved with the EcLiPSE trial) at the CTRC. Participants are randomised to levetiracetam or phenytoin in a ratio of 1:1. Randomisation is stratified by centre for logistical purposes only. Sequentially numbered randomisation packs were provided for each ED. Details of block sizes can be found in the Statistics Trial File under section 4.

8.11 Sequence and duration of all study periods

A schematic of the study design can be found in section 1 of the study protocol. A table of trial assessments can be found in section 8.1 of the protocol.

To summarise this information, the child is admitted into the ED with CSE that fails to respond to first-line treatment. Once the child has been screened and assessed as eligible, they are entered into EcLiPSE and randomised to either levetiracetam or phenytoin and the treatment is administered. Once the child has stopped seizing, consent will be sought from the parent/legal representative at an appropriate time (usually within 24 hours of treatment).

CRF "Form 1: Randomisation & Second Line Treatment" is to be completed during the seizure in the ED. CRF: "Form 2: Follow-up" can be completed retrospectively from the participant's medical notes. 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. This is to be completed by the patients/parents/legal representatives and returned to the CTU. Further details can be found in section 8.3.1 of the protocol.

8.12 Schedule of assessments

A full schedule of trial assessments and timeline of data collection can be found in section 8.1 of the protocol.

9. Listing of Outcomes

9.1 Primary outcome

The primary outcome is the time to cessation of all visible signs of convulsive seizure activity, calculated from the time of randomisation.

9.2 Secondary outcomes

The secondary outcomes are:

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.

10. Determination of Sample Size

The sample size calculation can be found in section 9.3 of the protocol. The required sample size will be 280 participants plus a 10% adjustment for loss to follow up.

11. Study Framework

The overall objectives for each of the study outcomes (primary and secondary) are to test the superiority of levetiracetam compared with phenytoin.

12. Confidence Intervals, p-values and Multiplicity

All applicable statistical tests will be two-sided and will be performed using a 5% significance level; confidence intervals presented will be 95%. No adjustment will be made for multiplicity for the secondary outcomes. P-values will be reported to 3 decimal places and all other values will be reported to 2 decimal places.

13. Timing and Objectives of Interim and Final Analyses

13.1. Interim monitoring and analyses

Details on interim analyses are compatible with those found in the protocol in section 9.4. The Independent Data and Safety Monitoring Committee (IDSMC) will meet at least annually as stated within section 5.3 of the IDSMC Charter. There are no formal interim analyses planned at any time during EcLiPSE. Should the IDSMC request an interim analysis, the Peto-Heybittle stopping rule will be applied. This requires an extreme p-value of $p<0.001$ as evidence to stop the trial for benefit or harm. This approach will be used to allow the IDSMC flexibility with the number and timings of further analyses based on current safety and efficacy data as it has the added benefit of preserving an overall two-sided type I error of 0.05 for the final analysis. However, recommendations and decisions around trial continuation will not be based on p-values alone.

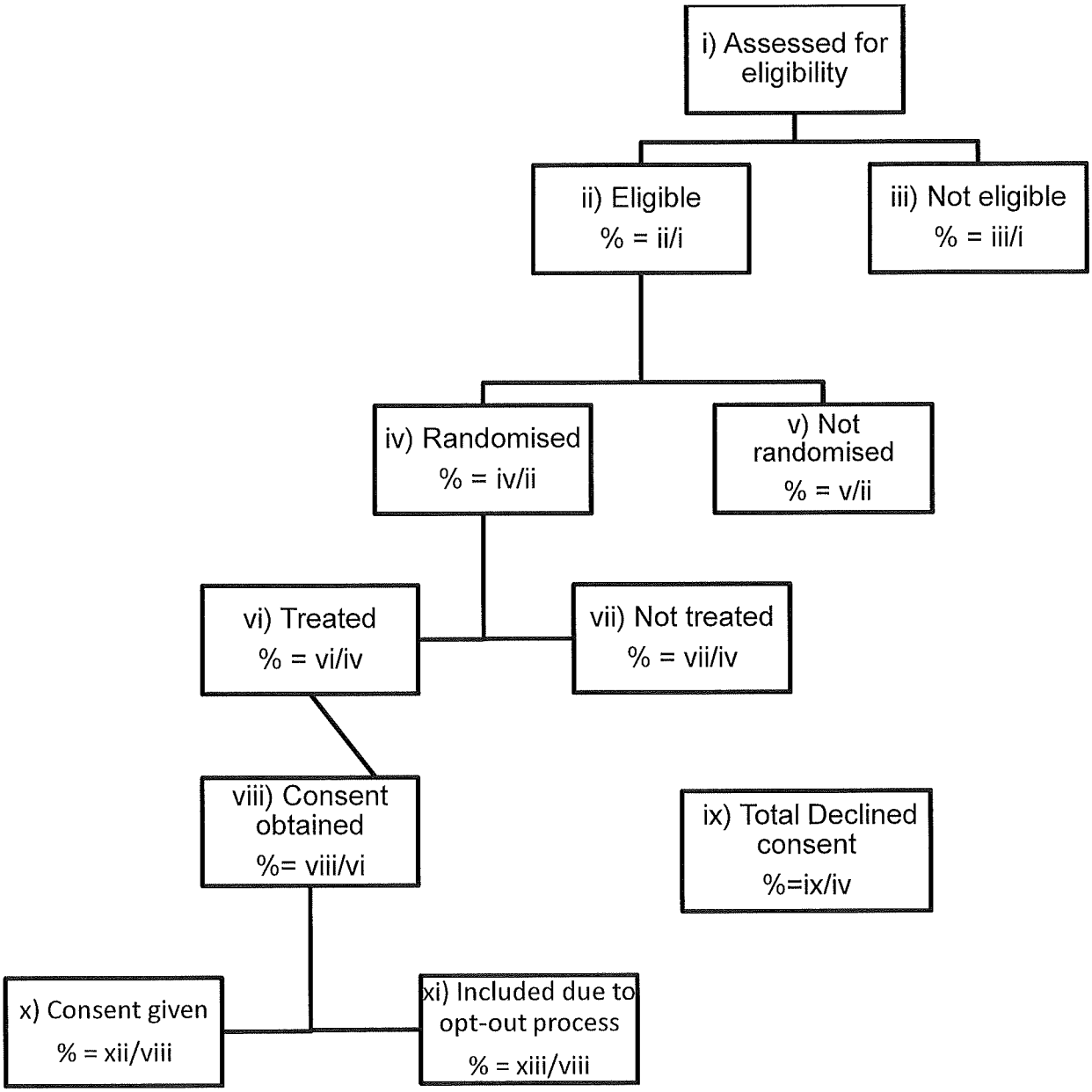
13.2. Final analysis

All outcomes will be analysed after the end of the trial, which is defined in section 8.7 of the protocol as "the date of database lock. This is the date on which data modification privileges are withdrawn from the trial database."

14. Disposition of Participants

14.1. Screening, eligibility and recruitment

Reporting of the flow of participants through the trial will be as follows, along with reasons for: not eligible; not randomised; not treated; not consented where available.



Screening forms will be summarised by site and overall in a table detailing:

Screening and eligibility

i) the number of patients who were assessed for eligibility when admitted to the ED,

ii) those who met the study inclusion criteria at screening (expressed as a frequency and a % with the denominator being i),

iv) those who were eligible at screening and were randomised (expressed as a frequency and a % with the denominator being ii),

Treatment

vi) those who were eligible at screening, randomised and treated, (expressed as a frequency and a % with the denominator being iv),

Consent

x) those who were treated and explicitly gave consent, (expressed as a frequency and a % with the denominator being viii),

ix) those who declined consent overall (expressed as a frequency and a % with the denominator being iv),

xi) those with opt-out consent, defined as those who were treated but not approached during hospital stay for consent, and did not respond to letters home (expressed as a frequency and a % with the denominator being viii),

The consent rate will be presented split between those who explicity gave consent (x) and those who consented through the opt out process (xi)

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. Screening will commence once a child has arrived in the ED with a convulsive seizure and has started first-line treatment. Data from these screening forms will be used to summarise the number of patients who were:

- Eligible/ineligible and randomised/not randomised (see points i – v in flow diagram above)
- Received the randomised allocation (expressed as a frequency and a % with denominator being viii)
- Did not receive the randomised allocation* (expressed as a frequency and a % with denominator being viii)

- Lost to follow-up* (expressed as a frequency and a % with denominator being viii)
- Randomised and included/excluded from the primary analysis (see points vi - xi flow diagram above).

*reasons will be provided.

Reasons for ineligibility will be summarised in a table with reasons for ineligibility as described in section 5 of the protocol. Frequencies will be presented along with percentages using the denominator as iii). Reasons for consent declined will be summarised in a table. Frequencies will be presented along with percentages using the denominator as ix). EcLiPSE uses an opt-out procedure, so if no consent form is returned to the CTU then they will still be included in the analyses.

Completeness of follow-up will be presented in the form of a CONsolidated Standards Of Reporting Trials (CONSORT) flow diagram. The number lost to follow up, not consented, and with missing data within each treatment group will be reported and the reasons where known will be documented. Recruitment summaries will be presented as a table split by site and overall along with a recruitment graph. This will include:

- Date of site opening
- Date of first randomisation
- Date of most recent randomisation
- Number treated (by arm and overall)

14.2. Post randomisation discontinuations

14.2.1 No second-line treatment administered

See section 8.7 for details for patients who were randomised but did not receive a second-line treatment.

14.2.2 Second-line treatment administered

As the primary outcome is collected when the patient is in the emergency department, it is anticipated that loss to follow up is most likely to impact the 14 day follow up completed after discharge.

As EcLiPSE uses deferred consent (taken after treatment, a single infusion, is given), it is not possible to withdraw from treatment. Therefore the levels of withdrawal are from:

- Continued follow up to day 14
- Complete withdrawal from study
- Withdrawal after randomisation but prior to treatment initiation (at parents request)

15 Protocol Deviations

Possible protocol deviations are specified as minor or major in the Data Monitoring Plan, this can be found in section 16.1 of the trial master file.
Protocol deviations are classified prior to requesting the treatment allocations and any analysis being performed. The number (and percentage) of patients with at least one major/minor/any protocol deviation will be summarised by site and in total by treatment group. The patients that are included in the intention to treat (modified ITT) analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken. There is no per protocol analysis planned.

Patients to be excluded from an analysis population (see section 17.1) will be defined in template ST001TEM04: Protocol deviations and data set definitions which will be agreed and approved prior to any release of randomisation code.

16 Unblinding

Not applicable as EcLiPSE is an open label study.

17 Efficacy Evaluations

17.1 Data Sets Analysed

The efficacy analysis will use the intention to treat principle as far as practically possible. These analyses will be conducted on all randomised participants for whom consent was obtained (including opt out process) and received a second-line treatment, in the group to which they were randomly allocated. A per protocol analysis is not anticipated.

The membership of the analysis set for each outcome will be determined and documented and reasons for participant exclusion will be given prior to the blind being broken and the randomisation lists being requested. Reasons for exclusion are provided in section 8.4.

17.2 Demographic and Other Baseline Characteristics

Patient baseline data will be presented descriptively for treated patients with respect to:

- age (overall and split by categories of: <23 months, 2-11 years and 12-17 years)
- gender (female/male)
- weight (overall and split by categories of: <12kg, 12kg – 36kg and >36kg)
- whether the index episode of CSE is their first seizure (yes/no)
- site of infusion (Dorsum of hand or foot/Antecubital fossa/Long saphenous vein/ Central/Other)
- type of presenting seizure (Generalised tonic-clonic/ Generalised clonic/Focal clonic)

These will be presented both overall and for each randomised group. The baseline values can all be found on CRF "Form 1: Randomisation & Second Line Treatment".

Categorical data will be summarised by numbers and percentages. Age and weight will be presented as medians and inter-quartile range (IQR). Minimum and maximum values will also be presented for continuous data. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

17.3 Adherence with treatment

For details on treatment adherence see section 8.3. Reasons for non-adherence will be presented in tables overall and split by treatment and expressed as a frequency and a percentage with the denominator being those who were randomised, treated and consented.

Additional anticonvulsants are permitted within the trial (such as paraldehyde). See section 7.8.1 of the protocol for further details.

17.4 Analysis of outcomes

17.4.1 Primary Outcome

The primary outcome is the time from randomisation to cessation of all visible signs of convulsive seizure activity.

17.4.1.1 Derivation

Time to cessation of all visible signs of convulsive seizure activity will be calculated from the time of randomisation. The time of randomisation and the time of seizure cessation can be found on CRF "Form 1: Randomisation & Second Line Treatment". This CRF also records whether RSI was administered following the first 2nd line treatment, or whether an additional second-line treatment (anticonvulsant) was given, and the time of both of these.

If the seizure has not terminated by the time the infusion is complete then either RSI is administered immediately or another second-line treatment is given. For patients who are administered RSI before seizure cessation, the time will be censored at time of RSI plus 12 hours (720 minutes), and patients who have died before seizure cessation will be censored at the time of death plus 48 hours (2880 minutes). The time of seizure cessation will be used regardless of additional second-line treatments being administered. The unit of time for the primary outcome will be in minutes.

17.4.1.2 Analysis

The primary outcome is a time to event and will be primarily analysed using the log-rank test and Kaplan-Meier curves presented with the numbers at risk at specified time points (e.g. every 4 hours) for each treatment group. Additional analysis adjusted for centre as a random

effect and the baseline characteristics of: weight, gender, whether it's their first seizure, site of infusion and whether additional anticonvulsants were given alongside the second-line treatment (with categories as defined in section 17.2) will be conducted using a Cox Proportional Hazards model. The point estimate and confidence interval will be presented alongside the p-value.

17.4.1.3 Partial missing data imputation

The primary outcome requires the time of randomisation and the time of seizure cessation. If the time of randomisation is unobtainable and infusion start time is available, randomisation time will be imputed as:

Infusion start time – median time of randomisation to infusion start for all patients.

If the infusion end time is unobtainable, infusion end time will be imputed as:

Infusion start time + median time to infusion end for each treatment group

If the time of seizure cessation is unobtainable, seizure cessation time will be imputed as:

Infusion end time + median time to seizure end for each treatment group.

17.4.2 Need for further anti anticonvulsant(s) to manage the seizure after the initial agent

17.4.2.1 Derivation

This includes information found on CRF "Form 2: Follow-up" on page 3 for the question "Was any further management needed in the 24 hours post second line treatment?" with a "yes/no" response, and also on "Form 1: Randomisation & Second Line Treatment" in section 7 for the question "Was an additional second-line IV treatment given?" with a "yes/no" response.

17.4.2.2 Analysis

This is a binary outcome and will be primarily analysed using the chi-square test, presented with relative risks. A logistic regression model adjusted for centre as a random effect and the baseline characteristics of: weight, gender, whether it's their first seizure, site of infusion and

whether additional anticonvulsants alongside the second-line treatment were given (with categories as defined in section 17.2) will be fitted as an additional analysis to the primary chi-squared test.

17.4.3 Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE.

17.4.3.1 Derivation

This can be found on CRF "Form 1: Randomisation & Second Line Treatment" in section 7 for the question "Was an RSI needed?" with a "yes/no" response.

17.4.3.2 Analysis

This is a binary outcome and will be analysed as per section 17.4.2.2.

17.4.4 Need to be admitted to critical care

17.4.4.1 Derivation

This can be found on CRF "Form 2: Follow-up" on page 5 for the question "Was patient admitted to critical care (HDU, PICU or ICU) at any time?" with a "yes/no" response.

17.4.4.2 Analysis

This is a binary outcome and will be analysed as per section 17.4.2.2.

17.4.5 Serious adverse reactions including death, airway complications, and cardiovascular instability (cardiac arrest, arrhythmia and hypotension requiring intervention), extravasation injury ('purple-glove syndrome'), extreme agitation

17.4.5.1 Derivation

Serious adverse reactions are defined in section 10.1.4 of the study protocol. If a patient experiences an SAR, this will be recorded on CRF: "Adverse events". This form specifies whether the AE is serious (an SAE) and includes a free text description of the event. Further information on any SAEs occurring can be found on CRF: "Serious adverse event report form". An SAE whose causal relationship to the study drug is assessed by the Chief Investigator as "possible", "probable", or "definite" is an SAR.

17.4.5.2 Analysis

No formal analysis will be undertaken for this outcome due to low number of events. SARs will be listed as per section 20.

18 Missing data and withdrawals

As both phenytoin and levetiracetam are administered as a single infusion and efficacy follow up is 24 hours, the levels of missing data for the primary outcome are expected to be low.

Levels of missing data for the 14 day follow-up questionnaire will be presented in a frequency table expressed as a frequency and a % with the denominator being those who were randomised, treated and consented.

The numbers (with reasons) of losses to follow-up and withdrawals over the course of the trial will be summarised by treatment arm. This will be presented in a CONSORT diagram alongside a table, with numbers and reasons for withdrawal and/or exclusion from analysis given. This will include withdrawal prior to treatment being initiated for reasons other than seizure stopping.

See section 17.4.1.3 for details of partial missing data imputations.

19 Additional Analyses

Sensitivity analyses outlined in sections 19.1 to 19.5 will be conducted to assess robustness. They will be considered robust if the direction of the effect is the same and confidence intervals largely overlap.

19.1 Additional analysis 1: Start time calculated from infusion

A sensitivity analysis will be undertaken which will analyse the time to cessation of all visible signs of convulsive seizure activity, calculated from the infusion start time (found on CRF "Form 1: Randomisation & Second Line Treatment") instead of from the time of randomisation. This will be used to test the robustness of the primary outcome when using the time to cessation of seizure from time of randomisation.

19.2 Additional analysis 2: non-treated exclusions

To compare the robustness of excluding those patients who were randomised but not treated, a sensitivity analysis will be performed censoring this patient population at time zero rather than excluding them from the analysis and using Kaplan Meier curves and the log rank test.

19.3 Additional analysis 3: Censoring at start of a 2nd second line treatment

A further analysis will be undertaken to investigate the effect of being administered any 2nd second-line treatment. In the main analysis the time of seizure cessation will be used regardless of additional second-line treatments being administered. For this sensitivity analysis patients will be censored at the point of the 2nd second-line treatment being administered.

19.4 Additional analysis 4: Competing risk of RSI

A further sensitivity analysis will be conducted to consider the robustness of the approach to the primary analysis. This will be done using Gray's test, Gray (1998), where RSI will be considered a competing risk, with seizure cessation the event of interest.

19.5 Additional analysis 5: partial missing primary outcome data imputation

A sensitivity analysis will be conducted to consider the effect of the imputations made (as described in section 17.4.1.3) on the patients analysed for primary outcome. Any patients who had imputed times for primary outcome will be excluded from the analysis.

20 Safety

Adverse events will be categorised according to severity as "Mild", "Moderate", or "Severe". They will also be classified in relation to the causality with the treatment as "Unrelated", "Unlikely", "Possibly", "Probably", and "Almost certainly". Full details on the definition and classification of these adverse events are presented in section 10 of the protocol.

Serious adverse events will be summarised and described descriptively and presented as line listings. No formal statistical tests will be undertaken. Summary tables will include frequencies of SAEs that:

- Result 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
- Consists of a congenital anomaly or birth defect
- Other important medical events

20.1 Data sets analysed

For the safety analysis, patients will be analysed according to which treatment was received in order to accurately represent the adverse effects of each treatment. There may be cases where patients receive phenytoin after levetiracetam or levetiracetam immediately after phenytoin. Therefore a third column will be presented for those patients who received both drugs.

20.2 Presentation of the data

Adverse and serious adverse events will be presented using descriptive statistics. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE will also be presented for each treatment arm. No formal statistical testing will be undertaken. SAEs will be presented as line listings.

21 Quality Control

To ensure quality control, an independent statistician will follow this SAP to independently program the primary outcome analysis from the raw data. Any discrepancies found will be discussed with the trial statistician to resolve. No programming will be shared or shown between the statisticians. The independent statistician will also check the report against their output obtained from the statistical software.

22 References

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- Raab GM, Day S, Sales J: How to select covariates to include in the analysis of a clinical trial. Control Clin Trials 2000, 21(4):330–342.
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23 Appendices

23.1 Appendix 1: TSC recommendations

EcLiPSE is a multi-centre, open label randomised controlled trial comparing intravenous levetiracetam with intravenous phenytoin in children who present with convulsive status epilepticus for the cessation of prolonged seizures which fail to respond to two doses of benzodiazepines.

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%. Successful seizure cessation has been reported to be 76-100%. 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.

Treatment failure and use of Rapid Sequence Intubation:

The clinical trial protocol states: If the patient continues to have seizures following administration of the randomised treatment they should be treated as directed by their local clinician.

In this situation the treating clinician may give the alternative second-line treatment followed by RSI if the seizure remains ongoing, or may use RSI without additional second-line intervention. RSI stops the seizure but is invasive and is considered a clinically negative outcome.

Monitoring of EcLiPSE has identified the use of RSI at a higher frequency of use than expected. Additionally, monitoring has identified that RSI may be administered before the randomised treatment has ended. In this scenario, the drug dose and time is insufficient to determine whether the seizure would have stopped had the drug been given in its entirety.

All participants will either experience seizure cessation in response to second-line treatment, or RSI. Death is extremely rare and is expected to have occurred only 2-3 times during EcLiPSE.

Statistical Analysis Plan

The current SAP treats RSI as an event with the time of the event inflated to allow for it being a negative outcome. However, the SAP was developed in advance of identifying the use of RSI prior to the end of the randomised treatment and the general frequency of its use.

This was raised as a concern by the trial statistics team at a meeting of the Independent Data and Safety Monitoring Committee (IDSMC). The IDSMC decided that the Trial Steering Committee (TSC) should consider the issue to protect trial validity as the decision of the TSC would be blind to any comparative data knowledge.

Informative censoring

While the primary outcome is seizure cessation, the interest is in cessation in response to the randomised second-line treatment.

Although the use of RSI means that seizure cessation occurs, it cannot be experienced as a result of second-line treatment. The need to administer RSI is a negative outcome for the child, while seizure cessation in response to a second-line treatment is a positive outcome.

The use of the log-rank test (the same method used within the sample size calculation) censors other event types at the time they occur and assumes that the competing event risks are independent.

This censoring is assumed to be non-informative and fails to consider that those who have experienced a competing event can never experience the event of interest.

Given that RSI is primarily administered in response to a failed second-line treatment, censoring at the time of RSI would be informative. To avoid informative censoring the current version of the SAP weighted the time of RSI (+24 hours) but treated it as an event. The concern with this is that treating it as an event will increase statistical power inappropriately.

Considerations: Competing risks

RSI may be considered a competing risk. In this situation seizure cessation in response to randomised treatment is the positive main event of interest with the negative competing event being RSI, primarily but not exclusively used in response to treatment failure.

Williamson et al (2006) point to the use of Gray's test as having greater statistical power than the log-rank test to detect treatment differences in settings where there are opposite effects for the two event types.

Grays test (1998), which is used to compare the cumulative subdistributional hazard assumes that if an individual experiences the competing event instead of the main event that their main event time is infinite. This would seem a reasonable assumption for EcLiPSE.

Sample size estimation

The power calculation for Grays test is heavily influenced by the values used for patient follow-up time and trial accrual. Inclusion of the trial accrual period is not appropriate for EcLiPSE where the length of patient follow-up is of a very short duration. To attempt to reflect this in the sample size calculations, this requires setting follow-up to 1 and accrual to 0. However, the accuracy of the power calculations under this extreme scenario may be questionable.

Therefore following discussions the decision is to:

1) Maintain the original sample size calculation as the conservative option given that Williamson et al (2006) concluded that this may have lower power than Gray's test
2) Revise the SAP so that the analysis is consistent with the principle of the subdistributional model (if the individual experiences the competing event instead of the main event that their main event time is infinite). Therefore if an RSI is administered then the patient is censored at the time of RSI + 12 hours. The majority of seizures are controlled within 40 minutes of randomisation.
3) Conduct a secondary analysis using Gray's test to consider the robustness of the approach to the primary analysis.

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