



## Clinical trial results:

### A randomised controlled trial of the ketogenic diet in the treatment of epilepsy in children under the age of two years

#### Summary

EudraCT number	2013-002195-40
Trial protocol	GB
Global end of trial date	30 September 2021

#### Results information

Result version number	v1 (current)
This version publication date	28 March 2023
First version publication date	28 March 2023

#### Trial information

##### Trial identification

Sponsor protocol code	13/0656
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02205931
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	UCL
Sponsor organisation address	Gower Street, , London, United Kingdom, WC1E 6BT
Public contact	Helen Cross, UCL - Institute of Child Health, 0044 2075994105, h.cross@ucl.ac.uk
Scientific contact	Helen Cross, UCL - Institute of Child Health, 0044 2075994105, h.cross@ucl.ac.uk

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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## Results analysis stage

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Analysis stage	Final
Date of interim/final analysis	24 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2021
Global end of trial reached?	Yes
Global end of trial date	30 September 2021
Was the trial ended prematurely?	No

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Notes:

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## General information about the trial

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Main objective of the trial:

To determine the effectiveness on seizure control of the ketogenic diet (KD) compared to further anti-epileptic drug (AED) treatment in children with epilepsy aged 3 months to 2 years who have failed to respond to two or more AEDs.

Research question:

Are there clear benefits in terms of seizure control in infants with continued seizures, despite two AEDs, treated with a KD as compared to a similar control group who are treated with a further AED?

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Protection of trial subjects:

Common side effects such as constipation, diarrhoea and vomiting, were minimised by manipulation of the diet. Rarely, renal stones occurred. Regular blood evaluation was done to ensure no potential electrolyte imbalance or mineral deficiency. Clinical laboratory assessments for haematology, biochemistry, and ketone assessment in blood and urine were carried out. Metabolic screening was done prior to start of trial to check that there were no contraindications to use of ketogenic diet.

The young age of many of the children recruited for this trial had an inpatient admission for initiation (the majority already were inpatients for the management of their epilepsy owing to the frequency of seizures).

At each of the centres, the paediatric neurologist worked with the dietetic team using a manualised dietetic care pathway for KD implementation.

The risk of blood tests were minimal:

- Sometimes a bruise developed where the needle was inserted. This was mitigated by pressing over the site with cotton wool for several minutes with the arm left straight (not bent).
- As with any wound, an infection may develop where the needle was inserted; this was very rare and was treated as per standard care.
- Rarely, some people feel fainted during a blood test and were treated with standard of care.

Some children were withdrawn from the treatment prior to 8 weeks as there was 50% increase in seizure frequency from baseline, or due to some other side effects.

Some children were reverted back to standard management when seizure control was not achieved on the KD arm by 8 weeks.

Children on the AED arm were prescribed further AEDs as per standard medical management.

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Background therapy:

Children were eligible if they had a diagnosis of epilepsy and had previously trialled on two anti epileptic medications; they were required to have stable AED doses during the baseline period and the duration of the 8 week primary outcome period

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Evidence for comparator:

Anti epileptic medication is standard treatment of epilepsy. Choice of medication will depend on type of seizure/epilepsy. During set up of the study a workshop involving PI representation from all sites was held, to determine consensus on the AEDs that would be utilised in each type of seizure/epilepsy to ensure consistency across sites

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Actual start date of recruitment	01 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 136
Worldwide total number of subjects	136
EEA total number of subjects	0

Notes:

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#### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	136
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

136 participants recruited from hospital-based paediatric neurology centres implementing the KD. PIC sites were also used to identify participants through patient records. Potential parents/guardians of participants were contacted initially by a member of their direct healthcare team and were sent invitation letter and PIS via post or email.

### Pre-assignment

Screening details:

Potential participants were identified at each site by direct healthcare team. Parents of eligible children were consented. Full history including seizure type, neurological examination, weight, length and head circumference were documented. Children requiring thickeners in their feed for reflux were included as there was no interaction with KD.

### Period 1

Period 1 title	Overall Trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial was open label randomised controlled multicentred.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Trial arm 1: Classical ketogenic diet (KD arm)

Arm description:

The experimental intervention will be 8 week trial of KD therapy. A KD Intervention Manual will be created and provided to sites to ensure consistency of the KD implementation across centres. The manual includes basic instructions on how to calculate the classical KD and advice regarding diet implementation, such as supplementation, tube feeding, breastfeeding, weaning and fine-tuning the diet. Children allocated to KD therapy will have their diets individually calculated by a paediatric dietitian with consideration of daily calorie requirements, adequate protein intake for growth and vitamin and mineral supplementation. All diets will be implemented according to a classical KD protocol, i.e. based on a ratio of fat to carbohydrate and protein that will usually be between 2:1 and 4:1. For ketosis meal plans have to accurately calculated for each child. Further adjustments to KD are determined by regular growth monitoring, seizure control and daily home measurement of urine and ketones

Arm type	Experimental
Investigational medicinal product name	Ketogenic diet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Oral use

Dosage and administration details:

N/A - Ketogenic diet

<b>Arm title</b>	Trial Arm 2: Further Anti-epileptic drugs (AED arm)
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Arm description:

The control intervention will be drug therapy with most appropriate further AED for a particular child, depending on their presenting seizures and syndrome and previous drugs used. This will be chosen by the expert clinician responsible for management of patient's epilepsy. Paediatric neurologists will meet at an initial workshop to discuss clinical practice with the aim to form the basis of a consensus protocol to ensure the consistency of AED treatments delivered. The Dietetic Assistant will monitor cross-site consistency of IMP prescription according to the protocol. A discussion about diet will be undertaken with families of infants randomised to the AED arm at randomisation visit. If participant already under local dietetic support, then monitoring will continue. If participant does not have local dietetic support but it is deemed necessary by the ketogenic dietitian, an appropriate referral will be made by clinician. Brief discussion about general nutrition will take place.

Arm type	Control Intervention
Investigational medicinal product name	Carbamazepine
Investigational medicinal product code	
Other name	Tegratol
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

100, 200, 400 mg tablets  
100mg/5ml oral suspension

Investigational medicinal product name	Clobazam
Investigational medicinal product code	
Other name	Frisium
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

5mg/5ml and 10mg/5ml oral suspension  
10mg tablets

Investigational medicinal product name	Clonazepam
Investigational medicinal product code	
Other name	Rivotril
Pharmaceutical forms	Oral drops, Oral solution
Routes of administration	Oral use

Dosage and administration details:

0.5 mg/5ml and 2mg/5ml oral solution  
2.5 mg/ml oral drops  
500 micrograms, 2 mg tablets

Investigational medicinal product name	Ethosuximide
Investigational medicinal product code	
Other name	Zarontin
Pharmaceutical forms	Capsule, Syrup
Routes of administration	Oral use

Dosage and administration details:

250mg capsules  
250mg/5ml syrup

Investigational medicinal product name	Lacosmide
Investigational medicinal product code	
Other name	Vimpat
Pharmaceutical forms	Syrup, Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg/ml syrup  
50, 100, 150, 250 mg tablets

Investigational medicinal product name	Lamotrigine
Investigational medicinal product code	
Other name	Lamictal
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

2mg, 5mg, 100 mg dispersible tablets

Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	
Other name	Keppra

Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use
Dosage and administration details: 100mg/ml oral solution 250mg, 500mg, 750mg, 1000mg tablets	
Investigational medicinal product name	Nitrazepam
Investigational medicinal product code	
Other name	Mogadon
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use
Dosage and administration details: 2.5mg/5ml oral suspension 5mg tablets	
Investigational medicinal product name	Phenytoin
Investigational medicinal product code	
Other name	Epanutin
Pharmaceutical forms	Capsule, Suspension for oral suspension, Tablet
Routes of administration	Oral use
Dosage and administration details: 25, 50, 100mg capsules 50mg infatabs 30mg/5ml suspension	
Investigational medicinal product name	Rufinamide
Investigational medicinal product code	
Other name	Inovelon
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use
Dosage and administration details: 100, 200, 400 mg tablets 40mg/ml oral suspension	
Investigational medicinal product name	Sodium Valproate
Investigational medicinal product code	
Other name	Epilim
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details: 200mg/5ml	
Investigational medicinal product name	Stiripentol
Investigational medicinal product code	
Other name	Diacomit
Pharmaceutical forms	Capsule, Oral powder in sachet
Routes of administration	Oral use
Dosage and administration details: 250mg and 500mg powder (sachets) 250mg and 500mg capsules	
Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	Topamax
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: 15mg, 25mg, 50mg sprinkle capsules 25mg, 50mg, 100mg tablets	

Investigational medicinal product name	Vigabatrin
Investigational medicinal product code	
Other name	Sabril
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

500mg powder (sachets)

Investigational medicinal product name	Zonisamide
Investigational medicinal product code	
Other name	Zonegran
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25mg, 50mg, 100mg capsules

<b>Number of subjects in period 1</b>	Trial arm 1: Classical ketogenic diet (KD arm)	Trial Arm 2: Further Anti-epileptic drugs (AED arm)
Started	78	58
Completed	43	32
Not completed	35	26
Wanted KD arm hence not received AED intervention	-	4
Consent withdrawn by subject	6	1
Physician decision	7	2
Withdrawn due to study ending	11	10
Elected for surgery	-	2
Lost to follow-up	2	2
Patient deceased	3	-
Randomised in error	-	1
Protocol deviation	6	4

## Baseline characteristics

### Reporting groups

Reporting group title	Trial arm 1: Classical ketogenic diet (KD arm)
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Reporting group description:

The experimental intervention will be 8 week trial of KD therapy. A KD Intervention Manual will be created and provided to sites to ensure consistency of the KD implementation across centres. The manual includes basic instructions on how to calculate the classical KD and advice regarding diet implementation, such as supplementation, tube feeding, breastfeeding, weaning and fine-tuning the diet. Children allocated to KD therapy will have their diets individually calculated by a paediatric dietitian with consideration of daily calorie requirements, adequate protein intake for growth and vitamin and mineral supplementation. All diets will be implemented according to a classical KD protocol, i.e. based on a ratio of fat to carbohydrate and protein that will usually be between 2:1 and 4:1. For ketosis meal plans have to accurately calculated for each child. Further adjustments to KD are determined by regular growth monitoring, seizure control and daily home measurement of urine and ketones

Reporting group title	Trial Arm 2: Further Anti-epileptic drugs (AED arm)
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Reporting group description:

The control intervention will be drug therapy with most appropriate further AED for a particular child, depending on their presenting seizures and syndrome and previous drugs used. This will be chosen by the expert clinician responsible for management of patient's epilepsy. Paediatric neurologists will meet at an initial workshop to discuss clinical practice with the aim to form the basis of a consensus protocol to ensure the consistency of AED treatments delivered. The Dietetic Assistant will monitor cross-site consistency of IMP prescription according to the protocol. A discussion about diet will be undertaken with families of infants randomised to the AED arm at randomisation visit. If participant already under local dietetic support, then monitoring will continue. If participant does not have local dietetic support but it is deemed necessary by the ketogenic dietitian, an appropriate referral will be made by clinician. Brief discussion about general nutrition will take place.

Reporting group values	Trial arm 1: Classical ketogenic diet (KD arm)	Trial Arm 2: Further Anti-epileptic drugs (AED arm)	Total
Number of subjects	78	58	136
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	78	58	136
Gender categorical Units: Subjects			
Female	39	22	61
Male	39	36	75

### Subject analysis sets

Subject analysis set title	Intention to treat analysis at 8 weeks-KD arm
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

78 patients started KD intervention. 11 withdrew before 8 weeks. 67 continued KD to 8 weeks. 6 patients not included in 8 week analysis as data missing/incomplete. 61 included in intention-to-treat analysis at 8 weeks.

Subject analysis set title	Intention to treat analysis at 12 months-KD arm
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

24 patients withdrew after 8 weeks before 12 months. 43 patients continued KD to 12 months. 12 patients not included in data analysis at 12 month due to missing/incomplete data. 31 patients included in intention to treat analysis at 12 months.

Subject analysis set title	Intention to treat analysis at 8 weeks-AED arm
Subject analysis set type	Intention-to-treat

Subject analysis set description:

53 patients started AED intervention. 4 patients withdrew after intervention before 8 weeks. 49 patients continued AED to 8 weeks. 2 patients not included in data analysis at 8 weeks due to missing/incomplete data. 47 included in intention to treat analysis at 8 weeks

Subject analysis set title	Intention to treat analysis at 12 months-AED arm
Subject analysis set type	Intention-to-treat

Subject analysis set description:

17 patients withdrew after 8 weeks before 12 months. 32 patients continued AED to 12 months. 7 patients not included in analysis due to missing incomplete data. 25 patients included in intention-to-treat analysis at 12 months.

<b>Reporting group values</b>	Intention to treat analysis at 8 weeks-KD arm	Intention to treat analysis at 12 months-KD arm	Intention to treat analysis at 8 weeks-AED arm
Number of subjects	61	31	47
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	61	31	47
Gender categorical Units: Subjects			
Female			
Male			

<b>Reporting group values</b>	Intention to treat analysis at 12 months-AED arm		
Number of subjects	25		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	25		
Gender categorical Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	Trial arm 1: Classical ketogenic diet (KD arm)
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Reporting group description:

The experimental intervention will be 8 week trial of KD therapy. A KD Intervention Manual will be created and provided to sites to ensure consistency of the KD implementation across centres. The manual includes basic instructions on how to calculate the classical KD and advice regarding diet implementation, such as supplementation, tube feeding, breastfeeding, weaning and fine-tuning the diet. Children allocated to KD therapy will have their diets individually calculated by a paediatric dietitian with consideration of daily calorie requirements, adequate protein intake for growth and vitamin and mineral supplementation. All diets will be implemented according to a classical KD protocol, i.e. based on a ratio of fat to carbohydrate and protein that will usually be between 2:1 and 4:1. For ketosis meal plans have to accurately calculated for each child. Further adjustments to KD are determined by regular growth monitoring, seizure control and daily home measurement of urine and ketones

Reporting group title	Trial Arm 2: Further Anti-epileptic drugs (AED arm)
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Reporting group description:

The control intervention will be drug therapy with most appropriate further AED for a particular child, depending on their presenting seizures and syndrome and previous drugs used. This will be chosen by the expert clinician responsible for management of patient's epilepsy. Paediatric neurologists will meet at an initial workshop to discuss clinical practice with the aim to form the basis of a consensus protocol to ensure the consistency of AED treatments delivered. The Dietetic Assistant will monitor cross-site consistency of IMP prescription according to the protocol. A discussion about diet will be undertaken with families of infants randomised to the AED arm at randomisation visit. If participant already under local dietetic support, then monitoring will continue. If participant does not have local dietetic support but it is deemed necessary by the ketogenic dietitian, an appropriate referral will be made by clinician. Brief discussion about general nutrition will take place.

Subject analysis set title	Intention to treat analysis at 8 weeks-KD arm
----------------------------	---

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

78 patients started KD intervention. 11 withdrew before 8 weeks. 67 continued KD to 8 weeks. 6 patients not included in 8 week analysis as data missing/incomplete. 61 included in intention-to-treat analysis at 8 weeks.

Subject analysis set title	Intention to treat analysis at 12 months-KD arm
----------------------------	---

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

24 patients withdrew after 8 weeks before 12 months. 43 patients continued KD to 12 months. 12 patients not included in data analysis at 12 month due to missing/incomplete data. 31 patients included in intention to treat analysis at 12 months.

Subject analysis set title	Intention to treat analysis at 8 weeks-AED arm
----------------------------	--

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

53 patients started AED intervention. 4 patients withdrew after intervention before 8 weeks. 49 patients continued AED to 8 weeks. 2 patients not included in data analysis at 8 weeks due to missing/incomplete data. 47 included in intention to treat analysis at 8 weeks

Subject analysis set title	Intention to treat analysis at 12 months-AED arm
----------------------------	--

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

17 patients withdrew after 8 weeks before 12 months. 32 patients continued AED to 12 months. 7 patients not included in analysis due to missing incomplete data. 25 patients included in intention-to-treat analysis at 12 months.

**Primary: no of seizures**

End point title	no of seizures
End point description:	seizure count in weeks 6 to 8 of the intervention period and in the baseline assessment period.
End point type	Primary
End point timeframe:	after 8 weeks treatment

<b>End point values</b>	Trial arm 1: Classical ketogenic diet (KD arm)	Trial Arm 2: Further Anti- epileptic drugs (AED arm)	Intention to treat analysis at 8 weeks-KD arm	Intention to treat analysis at 8 weeks- AED arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	61	47	61	47
Units: number				
median (inter-quartile range (Q1-Q3))	3 (2 to 11)	5 (1 to 16)	3 (2 to 11)	5 (1 to 16)

**Statistical analyses**

<b>Statistical analysis title</b>	Poisson mixed model
Comparison groups	Intention to treat analysis at 8 weeks-KD arm v Intention to treat analysis at 8 weeks-AED arm
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	incident rate ratio
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	2.11

**Secondary: Seizure freedom**

End point title	Seizure freedom
End point description:	% those analysed free of seizures for weeks 6-8.
End point type	Secondary
End point timeframe:	8 weeks

<b>End point values</b>	Intention to treat analysis at 8 weeks-KD arm	Intention to treat analysis at 8 weeks-AED arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	47		
Units: number	7	6		

### Statistical analyses

<b>Statistical analysis title</b>	Logistic regression
Comparison groups	Intention to treat analysis at 8 weeks-KD arm v Intention to treat analysis at 8 weeks-AED arm
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	2.8

### Secondary: Responder rate

End point title	Responder rate
End point description:	
End point type	Secondary
End point timeframe:	
8 weeks	

<b>End point values</b>	Intention to treat analysis at 8 weeks-KD arm	Intention to treat analysis at 12 months-KD arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	47		
Units: number	28	19		

### Statistical analyses

<b>Statistical analysis title</b>	Logistic regression
Comparison groups	Intention to treat analysis at 8 weeks-KD arm v Intention to treat analysis at 12 months-KD arm
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.65

### Secondary: Tolerability

End point title	Tolerability
End point description:	
End point type	Secondary
End point timeframe:	
8 weeks	

<b>End point values</b>	Intention to treat analysis at 8 weeks-KD arm	Intention to treat analysis at 8 weeks-AED arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	47		
Units: Side effect score				
median (inter-quartile range (Q1-Q3))	40 (38 to 42)	41 (39 to 44)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of life

End point title	Quality of life
End point description:	
Child overall health score	
End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Intention to treat analysis at 12 months-KD arm	Intention to treat analysis at 12 months-AED arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	25		
Units: Score				
median (inter-quartile range (Q1-Q3))	60 (30 to 60)	30 (30 to 60)		

### Statistical analyses

<b>Statistical analysis title</b>	Mixed linear regression
Comparison groups	Intention to treat analysis at 12 months-KD arm v Intention to treat analysis at 12 months-AED arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	coefficient
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	15.17

### Secondary: Vineland neurodevelopmental score

End point title	Vineland neurodevelopmental score
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Intention to treat analysis at 12 months-KD arm	Intention to treat analysis at 12 months-AED arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	11		
Units: Score				
median (inter-quartile range (Q1-Q3))	41 (39 to 43)	40 (39 to 41)		

## Statistical analyses

<b>Statistical analysis title</b>	linear regression
Comparison groups	Intention to treat analysis at 12 months-KD arm v Intention to treat analysis at 12 months-AED arm
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	coefficient
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.34
upper limit	5.67

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 months

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	2.1
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### Reporting groups

Reporting group title	Trial arm 1: Classical ketogenic diet (KD arm)
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Reporting group description:

The experimental intervention will be 8 week trial of KD therapy. A KD Intervention Manual will be created and provided to sites to ensure consistency of the KD implementation across centres. The manual includes basic instructions on how to calculate the classical KD and advice regarding diet implementation, such as supplementation, tube feeding, breastfeeding, weaning and fine-tuning the diet. Children allocated to KD therapy will have their diets individually calculated by a paediatric dietitian with consideration of daily calorie requirements, adequate protein intake for growth and vitamin and mineral supplementation. All diets will be implemented according to a classical KD protocol, i.e. based on a ratio of fat to carbohydrate and protein that will usually be between 2:1 and 4:1. For ketosis meal plans have to accurately calculated for each child. Further adjustments to KD are determined by regular growth monitoring, seizure control and daily home measurement of urine and ketones

Reporting group title	Trial Arm 2: Further Anti-epileptic drugs (AED arm)
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Reporting group description:

The control intervention will be drug therapy with most appropriate further AED for a particular child, depending on their presenting seizures and syndrome and previous drugs used. This will be chosen by the expert clinician responsible for management of patient's epilepsy. Paediatric neurologists will meet at an initial workshop to discuss clinical practice with the aim to form the basis of a consensus protocol to ensure the consistency of AED treatments delivered. The Dietetic Assistant will monitor cross-site consistency of IMP prescription according to the protocol. A discussion about diet will be undertaken with families of infants randomised to the AED arm at randomisation visit. If participant already under local dietetic support, then monitoring will continue. If participant does not have local dietetic support but it is deemed necessary by the ketogenic dietitian, an appropriate referral will be made by clinician. Brief discussion about general nutrition will take place.

<b>Serious adverse events</b>	Trial arm 1: Classical ketogenic diet (KD arm)	Trial Arm 2: Further Anti-epileptic drugs (AED arm)	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 78 (100.00%)	58 / 58 (100.00%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Shunt malfunction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Adenotonsillectomy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy			
subjects affected / exposed	1 / 78 (1.28%)	4 / 58 (6.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagogastric fundoplasty			
subjects affected / exposed	0 / 78 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculo-peritoneal shunt			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infantile spasms			

subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	15 / 78 (19.23%)	10 / 58 (17.24%)	
occurrences causally related to treatment / all	0 / 46	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	4 / 78 (5.13%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 78 (1.28%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Immune system disorders</b>			
<b>Dermatitis allergic</b>			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
<b>coffee ground vomiting</b>			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Diarrhoea</b>			
subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haematemesis</b>			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Melaena</b>			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Varices oesophageal</b>			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vomiting</b>			
subjects affected / exposed	2 / 78 (2.56%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal</b>			

disorders			
Apnoea			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiration abnormal			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			

subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Respiratory depression</b>			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory disorder</b>			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory failure</b>			
subjects affected / exposed	1 / 78 (1.28%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Wheezing</b>			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Adenoiditis</b>			
subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bronchiolitis</b>			
subjects affected / exposed	3 / 78 (3.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bronchitis</b>			
subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ear infection</b>			

subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	11 / 78 (14.10%)	6 / 58 (10.34%)	
occurrences causally related to treatment / all	0 / 22	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	3 / 78 (3.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 78 (7.69%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 78 (3.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			

subjects affected / exposed	3 / 78 (3.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	4 / 78 (5.13%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral tonsillitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Blood ketone body			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketosis			

subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Malnutrition</b>			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolic acidosis</b>			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Weight gain poor</b>			
subjects affected / exposed	1 / 78 (1.28%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dehydration</b>			
subjects affected / exposed	2 / 78 (2.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Trial arm 1: Classical ketogenic diet (KD arm)	Trial Arm 2: Further Anti-epileptic drugs (AED arm)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 78 (92.31%)	54 / 58 (93.10%)	
<b>Nervous system disorders</b>			
<b>Seizure cluster</b>			
subjects affected / exposed	2 / 78 (2.56%)	3 / 58 (5.17%)	
occurrences (all)	2	3	
<b>Seizure</b>			
subjects affected / exposed	9 / 78 (11.54%)	10 / 58 (17.24%)	
occurrences (all)	12	13	
<b>Somnolence</b>			

subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 3	3 / 58 (5.17%) 3	
General disorders and administration site conditions			
Lethargy			
subjects affected / exposed	0 / 78 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	3	
Pyrexia			
subjects affected / exposed	7 / 78 (8.97%)	10 / 58 (17.24%)	
occurrences (all)	9	15	
Feeling abnormal			
subjects affected / exposed	0 / 78 (0.00%)	4 / 58 (6.90%)	
occurrences (all)	0	7	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 78 (15.38%)	4 / 58 (6.90%)	
occurrences (all)	13	5	
Diarrhoea			
subjects affected / exposed	7 / 78 (8.97%)	4 / 58 (6.90%)	
occurrences (all)	8	8	
Abdominal pain			
subjects affected / exposed	3 / 78 (3.85%)	1 / 58 (1.72%)	
occurrences (all)	4	1	
Teething			
subjects affected / exposed	10 / 78 (12.82%)	4 / 58 (6.90%)	
occurrences (all)	16	51	
Vomiting			
subjects affected / exposed	11 / 78 (14.10%)	11 / 58 (18.97%)	
occurrences (all)	13	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 78 (10.26%)	5 / 58 (8.62%)	
occurrences (all)	9	7	
Nasopharyngitis			
subjects affected / exposed	6 / 78 (7.69%)	7 / 58 (12.07%)	
occurrences (all)	9	9	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 4	4 / 58 (6.90%) 6	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 4	6 / 58 (10.34%) 6	
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all)	10 / 78 (12.82%) 11	11 / 58 (18.97%) 17	
Tonsillitis subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 4	1 / 58 (1.72%) 4	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 3	3 / 58 (5.17%) 3	
Viral infection subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 4	3 / 58 (5.17%) 3	
Metabolism and nutrition disorders Hyperketosis subjects affected / exposed occurrences (all)	7 / 78 (8.97%) 7	1 / 58 (1.72%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2014	Response to grounds of non-acceptance (dated 11th Aug 2014) from the MHRA. Changes to Protocol to reflect information in line with the above request-exclusion criteria
08 May 2015	<ol style="list-style-type: none"> <li>1. Ketones are to be recorded for both groups of infants.</li> <li>2. KIWE Side Effects, Seizure Diary and Food Diary updated.</li> </ol>
07 September 2015	<ol style="list-style-type: none"> <li>1. The addition of P.I.C sites: Dr Andrea Whitney, University Hospital Southampton NHS Foundation Trust and Dr Archana Desurkar, Sheffield Teaching Hospitals NHS Foundation Trust</li> <li>2. Update of contact details for CI and TM; Schematic trial design flowchart to include seizure recording frequency (Protocol v4.0 and Research site PIS v2.0)</li> <li>3. Clarification of procedures within the main text and flowchart of assessments within the protocol.</li> </ol>
12 November 2015	<ol style="list-style-type: none"> <li>1. Protocol - Reducing seizure frequency to greater than or equal to 4 seizures/week; If the child is prone to particularly frequent seizures in excess of 2/day then minimum one week baseline would be considered to suffice instead of 2 weeks; +/-5 days deviation window allowed at randomisation, 4 weeks and 8 weeks</li> <li>2. Removal of "β hydroxybutyrate and acetoacetate" as not required as part of haematology.</li> <li>3. Minor changes to the schematic of trial design, study procedures and schedule of assessments and flowchart of study assessments to reflect the trial procedures more accurately.</li> <li>4. MHRA amendment - There has been updated reference safety information for the following SPC's: SmPC Vigabatrin (ROT June 2014), SmPC Sodium Valporate (ROT March 2015), SmPC Phenytoin infatabs (ROT August 2015), SmPC levetiracetam (ROT August 2015), SmPC Lamotrigine (ROT July 2015), SmPC lacosamide (ROT October 2014), SmPC ethosuximide syrup (ROT July 2014), SmPC ethosuximide caps (ROT May 2015)</li> </ol>
07 November 2016	<ol style="list-style-type: none"> <li>1. Reducing the inclusion age from 3 months – 24 months to 1 month – 24 months.</li> <li>2. Removing the Month 3 visit, and thus after the Week 8 visit, the patients will be followed up at 6, 9, and 12 months only.</li> <li>3. Optionally, the week 4 visit can be conducted over the telephone.</li> <li>4. Special assay to be taken at baseline rather than at randomisation for patients on both arms, to avoid getting bled twice.</li> <li>5. Widening the visit windows for months 6, 9, and 12 to +/- 2 weeks.</li> <li>6. Adding new sites to the protocol including St Georges Hospital, Sheffield Teaching Hospitals, The Newcastle upon Tyne Hospitals, Lancashire Teach Hospitals, University Hospital Southampton and Leicester Royal Infirmary</li> <li>7. Changing the addresses for the CI, Trial Manager and Dietetic Assistant.</li> <li>8. Clarifying the routine blood tests to be taken</li> <li>9. Amending the seizure diary to include medication changes and weight recordings (optional)</li> <li>10. Adding emergency contact information on the patient information sheet</li> </ol>

16 May 2017	<ol style="list-style-type: none"> <li>1. Change of PI at Leicester and Bristol hospitals</li> <li>2. Removal of co-investigators in protocol</li> <li>3. Removal of Matthew's Friends as a recruiting centre</li> <li>4. Clarification of wording</li> <li>5. Notification of previous change in food diary</li> </ol>
02 January 2018	<ol style="list-style-type: none"> <li>1. Updates to the reference safety information for the following SPCs: Levetiracetam, Phenytoin infatabs, Rufinamide, Sodium Valproate, Epilim 400mg Powder and Solvent for solution for injection/infusion, Topiramate and Zonisamide.</li> <li>2. A no cost extension to recruitment to end on 31 October 2018.</li> </ol>
25 March 2019	<ol style="list-style-type: none"> <li>1. Recruitment end date on 30 April 2021.</li> <li>2. Manchester PI updated from Dr Timothy Martland to Dr Jeen Tan</li> <li>3. Protocol - amended the wording of exclusion criterion 11 on page 20 for protocol clarification – so patients who have been prescribed Phenobarbital are not excluded.</li> <li>4. Trial Manager updated from Siobhan Titre-Johnson to Dr Laura Lyons.</li> <li>5. Maryam Balogun added as the Research Administrator to the trial team.</li> <li>6. Sponsor details updated to remove Nimrita Verma and include Misha Ladva</li> </ol>
14 June 2019	<ol style="list-style-type: none"> <li>1. Addition of two research sites in England:</li> <li>2. Dr Manish Prasad, Nottingham University Hospitals NHS Trust</li> <li>3. Dr Rohini Rattihalli, Oxford University Hospitals NHS Foundation Trust</li> <li>4. Addition of four research sites in Scotland: <ul style="list-style-type: none"> <li>- Dr Elma Stephen, Royal Aberdeen Children's Hospital - NHS Grampian</li> <li>- Professor Andreas Bruncklaus, Royal Hospital for Children - NHS Greater Glasgow and Clyde</li> <li>- Prof Martin Kirkpatrick, Tayside Children's Hospital - NHS Tayside (Dundee)</li> <li>- Dr Ailsa McLellan, Royal Hospital for Sick Children - NHS Lothian (Edinburgh)</li> </ul> </li> </ol>
21 April 2020	<p>SmPC updates as follows:</p> <p>Tegretol (carbamazepine) Liquid 100mg, Novartis Pharmaceuticals UK Limited</p> <p>Tegretol (carbamazepine) 100mg,200mg,400mg tablets, Novartis Pharmaceuticals UK Limited</p> <p>Frisium (clobazam) 10mg tablets, Sanofi</p> <p>Clonazepam 2mg/5ml oral, Rosemont Pharmaceuticals Limited</p> <p>Clonazepam 0.5mg/5ml oral, Rosemont Pharmaceuticals Limited</p> <p>Zarontin (ethosuximide) 250mg, previously Pfizer Limited and now Aristo Pharma Limited</p> <p>Vimpat (lacosamide) 50 mg 100 mg 150 mg 200mg film-coated tablets, UCB Pharma Limited</p> <p>Lamictal (lamotrigine) 25/50/100/200mg tablets, GlaxoSmithKline UK</p> <p>Keppra (levetiracetam) 250 mg film-coated tablets, UCB Pharma</p> <p>Epilim (sodium valproate) 400mg Powder and Solvent, Sanofi</p> <p>Topamax (topiramate) 25mg tablets, Janssen-Cilag Ltd</p> <p>Sabril (vigabatrin) 500 mg film, Sanofi</p>

06 July 2020	<ol style="list-style-type: none"> <li>1. Consent can be taken over the phone with confirmation of consent via email or post and signature gained at the next face – to – face visit.</li> <li>2. Existing bloods which are less than 6 weeks old can be used for screening.</li> <li>3. Visits may be carried out remotely and data such as diaries and questionnaires can be collected via remote methods such as email, post or over the phone.</li> <li>4. Flexibility window for visits has been increased.</li> <li>5. Bloods may be taken locally (e.g. participants GP or local hospital) and results sent to the site.</li> <li>6. A contingency plan has been added if the central lab is unable to accept new samples. The sites will store the samples until the lab is ready to reopen."</li> </ol>
31 March 2021	<ol style="list-style-type: none"> <li>1. Protocol update regarding informed consent procedure obtained during a telephone consultation.</li> <li>2. Update of the RSI of the following SmPCs: Carbamazepine tablets (Tegretol) 100mg/200mg/400 mg tablets Clobazam Oral suspension 5 mg/5ml and 10mg/5ml Clobazam (Frisium) 10mg tablets Clonazepam Rivotril 0.5mg tablets Levetiracetam (Keppra) 250/500/750/1000 mg film-coated tablets, 100 mg/ml, oral solution, 100 mg/ml concentrate for solution for infusion Nitrazepam tablets (Mogadon 5mg tablets) Rufinamide (Inovelon) 100/200/400 mg film-coated tablets, 40 mg/ml oral suspension Topiramate (Topamax) 25mg, 50mg, 100mg film-coated tablets; 15mg, 25mg, 50mg sprinkle capsules; Vigabatrin (Sabril 500mg film-coated tablets)</li> <li>3. An extension to the recruitment period to end on 31 September 2021 and trial end date to 28 February 2022</li> <li>4. Edit of Trial Manager email address on protocol"</li> </ol>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: