Full title of trial	A randomised controlled trial of the ketogenic diet in the treatment of epilepsy in children under the age of two years
Short title	Ketogenic diet in infants with epilepsy (KIWE)
Version and date of protocol	Version 9.0 28 June 2020
Sponsor:	University College London (UCL)
Sponsor protocol number	13/0656
Funder (s) :	NIHR EME
EudraCT no	2013-002195-40
ACTIVE IMP(s):	Carbamazepine, Clobazam, Clonazepam, Ethosuximide, Lacosmide, Lamotrigine, Levetiracetam, Nitrazepam, Phenytoin, Sodium Valproate, Stiripentol, Topiramate, Vigabatrin, Zonisamide, Rufinamide
PLACEBO IMP(s):	None
Phase of trial	Phase IV
Sites(s)	Multisite

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Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief Investigator
Professor J Helen Cross

Signature Date

Sponsor Representative
Rajinder Sidhu

Signature Date

Contents

List of abbreviations

AE	Adverse Event
AED	Antiepileptic Drug
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
KD	Ketogenic Diet
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment

SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Trial personnel

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2 Summary

Title:	A randomised controlled trial of the ketogenic diet in the treatment of epilepsy in children under the age of two years
Short title:	Ketogenic diet in infants with epilepsy (KIWE)
Trial medication:	Carbamazepine, Clobazam, Clonazepam, Ethosuximide, Lacosmide, Lamotrigine, Levetiracetam, Nitrazepam, Phenytoin, Sodium Valproate, Stiripentol, Topiramate, Vigabatrin, Zonisamide, Rufinamide
Phase of trial:	Therapeutic Use (Phase IV)
Objectives:	The project aims to determine the effectiveness on seizure control of the ketogenic diet (KD) compared to alternative further anti-epileptic drug (AED) treatment in children with epilepsy aged 1 month to 2 years who have failed to respond to two or more pharmacological treatments.
Type of trial:	Open Label Randomised Control Trial (RCT)
Trial design and methods:	Eligible children (age 1 month to 2 years with epilepsy) will undergo baseline assessment, including medical and seizure history, neurological and anthropometric examination, administration of quality of life and developmental questionnaires, and biochemical investigations. They will then start a one or two week observation period with documentation of seizure frequency. Randomisation will occur on Day 8 or Day 15 for them to receive the KD or a further AED; the allocated treatment will commence on the day of randomisation, with instruction and training. A second assessment (4 weeks after start of treatment) will include clinical review and questionnaire on tolerability (modified Hague scale of side effects). Assessments will be repeated at 8 weeks after the start of treatment including biochemical investigations, after which, according to patient response, KD (diet group) or AED (standard AED group) will then be continued or changed. Those in the AED group who have failed to achieve seizure control at the 8 week assessment will then be offered KD outside the context of the trial, depending on centre-specific waiting lists. Those in the KD arm who fail to achieve seizure control will be changed to standard clinical management, All patients will be followed up for 12 months from randomisation for retention, seizure outcome and neurodevelopmental status.
Trial duration per participant:	12 months
Estimated total trial duration:	4 years

Planned trial sites:	Multi-site
Total number of participants planned:	160
Main inclusion/exclusion criteria:	*Main inclusion criteria:* Children aged between 1 month and 24 months of age (not beyond second birthday at baseline) with a confirmed diagnosis of epilepsy. At least an average of 4 seizures/week and previous trial of two anti-epileptic drugs. *Main exclusion criteria:* Metabolic disease contraindicating use of the KD, e.g. pyruvate carboxylase deficiency, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Progressive neurological disease, severe gastroesophageal reflux or previous treatment with the KD.
Statistical methodology and analysis:	The primary outcome will be seizure count in weeks 6 to 8 of the intervention period compared to the baseline assessment period. Data will be analysed using a Poisson mixed model to account for clustering by centre (synonymous with therapist). The randomised allocation will be entered into the model as a fixed effect as will an indicator of time point (baseline or end of study), whilst the centre (trial site) will be included as a random effect.

3 Introduction

3.1 Background

Epilepsy is a condition where individuals are prone to recurrent epileptic seizures, a change in behaviour or movement that is the direct result of a primary change in the electrical activity in the brain. It is not a single condition -there are many different underlying causes and, more accurately, they should be referred to as the epilepsies. Up to 65% of individuals with epilepsy will have seizures controlled with antiepileptic drugs or enter spontaneous remission in their lifetime; however, this leaves 35% who will continue with seizures despite treatment. Standard first line management of an individual presenting with epilepsy is antiepileptic medication, judged on the basis of the type of epilepsy. Although guidelines exist on which drug to use (e.g. www.nice.org.uk/cg137) management is still based on a 'trial and error' approach. When the type of epilepsy is unclear it can be difficult to optimise treatment at the outset.

The incidence of epilepsy is greatest in the first two years of life (56-88/100,000 children/year) (Eltze *et al.*, 2013), a population who remain most at risk for neurodevelopmental compromise in the longer term. Early control of seizures is associated with better developmental outcome (Freitag and Tuxhorn, 2005) but, unfortunately, many of the epilepsies presenting in infancy are associated with a poor prognosis for seizure control (Chevrie and Aicardi, 1978). Few data are available with regard to effective treatments and, even where seizure freedom is achieved, this is unlikely to be sustained long-term (Altunbaşak *et al.*, 2007). This group of children therefore place a large burden on NHS services, with a need for regular clinical review and ongoing medication, as well as clinical and therapy support. This is especially true for those who remain resistant to medication, this group being amongst the most costly for medical and care services long term. It is therefore imperative that all other treatment options are explored as early as possible.

Epilepsy in this age group also remains a poorly defined entity; very few can be classified into an epilepsy syndrome and diagnosis of underlying cause remains difficult. Over 50% of infants presenting with seizures will have infantile spasms. This affects approximately 1 in 2000 infants; first-line treatment options (corticosteroids or vigabatrin) lead to seizure freedom in up to 70% of cases (Lux *et al.*, 2004) but side effects limit their duration of use and relapse rates are not insignificant (40%) (Lux *et al.*, 2005). Further, those who fail these treatments are limited in their treatment options. Of the remaining types of epilepsy, the majority are resistant to medication. There is little evidence on which to base our decisions on specific AED use in this young age group. Epidemiological data have shown this group to be the least likely to achieve longer term remission of up to two years (Berg *et al.*, 2001).

3.2 Rationale and risks/benefits

The ketogenic diet (KD) is a high-fat, low-carbohydrate diet designed to mimic the effects on the body of starvation. The main energy intake is fat, which is utilised in the body and produces ketones. The KD has been shown to be successful in controlling seizures in

many observational studies. A systematic review in 2006 determining 14 uncontrolled observational studies with at least 6 months follow up, found that 15.6% became seizure free and 33% had 50% or more seizure reduction (Keene, 2006). A statistical meta-analysis of 19 observational studies determined that the KD reduced seizures by over 90% in a third of the patients, regardless of age, seizure type, or aetiology; the pooled odds ratio of treatment success among patients staying on the diet relative to those discontinuing the diet was 2.25 (Henderson *et al.*, 2006). A recurrent concern expressed, however, in both reviews was the lack of Randomised Controlled Trial (RCT) data.

Our group has since published the first RCT of the KD, demonstrating effectiveness in children age 2-16 years (Neal *et al.*, 2008). In this trial, 145 children aged 2-16 years, who had failed at least two AEDs and had at least 7 seizures weekly were randomized to receive a KD, either immediately or after a 3-month delay with no additional treatment changes (the latter being the control group). After 3 months, the mean percentage of baseline seizures (on an intention to treat analysis) was significantly lower in the diet group (62%) than in the controls (137%, P <0.0001). Twenty-eight (38%) of the diet group had greater than 50% seizure reduction, compared to 4 (6%) controls (p<0.0001). This study was included in a recent Cochrane review (Levy *et al.*, 2012) on dietary treatments for epilepsy which concluded that the KD results in short to medium benefits in seizure control, with effects comparable to modern AEDs.

Open label observational data suggest that the KD is particularly effective in younger children. Retrospective studies have shown it to be an effective and well-tolerated treatment for infants (Caraballo *et al.*, 2011;Eun *et al.*, 2006;Kossoff *et al.*, 2002;Nordli *et al.*, 2001;Rubenstein *et al.*, 2005), with one study reporting significant improvements in infantile spasms and fewer side effects when the diet was used as an alternative first-line therapy to adrenocorticotrophic hormone (ACTH) (Kossoff *et al.*, 2008). Questions however remain; in children < 2 years of age, is the diet similar or better in effectiveness to medication when drugs have failed and how practical is its implementation? It is a treatment requiring a high degree of resources; implemented by a team comprised at least of an experienced paediatric neurologist and dietitian. The diet is patient specific, calculated according to calorie requirements and monitored thereafter, with ‘fine tuning’ required. It is imperative that the effectiveness and safety of the KD in this very young age group is now studied in a well-designed clinical trial.

Despite its name, the efficacy of the KD cannot be explained solely by brain ketone body accumulation. Various mechanisms with regard to its action have consequently been proposed (Masino and Rho, 2012). Of particular interest to us are the potential role medium chain fatty acids play in the effect of the KD. In experimental animals, the KD leads to mitochondrial biogenesis, alterations in brain energy metabolism and a consequent elevation of the seizure threshold (Bough *et al.*, 2006). However, neither the mechanism for this mitochondrial proliferation nor the metabolic changes associated with such changes are currently known. In addition to causing an elevation of ketones, the KD increases the plasma concentration of medium chain fatty acids(Heales *et al.*, 1991). Furthermore, such an increase in plasma concentration will lead to increased brain availability as medium chain fatty acids are transported across the blood brain barrier (Ebert *et al.*, 2003;Spector, 1988). In the younger child, there is evidence that a switch to fatty acid oxidation is undertaken more readily than in older children (Heales *et al.*, 1994). The increased availability of medium chain fatty acids has, so far, received little attention. However, it is reported that fatty acids can influence mitochondrial function (Wojtczak and Schönfeld, 1993). Recent work in our group (funded by Vitaflo) has demonstrated that medium chain fatty acids, particularly C10, may enhance neuronal mitochondrial function by stimulating mitochondrial proliferation. Medium chain fatty acids, particularly C10, have

also been shown more recently to have an antiepileptic effect (Chang *et al.*, 2013). These data raise the possibility that C10 alone has the ability to mimic aspects of the KD. Whether this has a role in a possible enhanced action of the KD in infancy should be determined and the biochemical basis for effectiveness identified.

We propose an RCT of infants comparing the efficacy of the KD to a further appropriate AED when a child has failed 2 AEDs, with a component to examine the possible role of medium chain fatty acids. The study would be the first of its kind in infants, and would make a significant contribution to the research evidence-base for treatment of infants with epilepsy.

3.3 Assessment and management of risk

This trial is categorised as Type A = No higher than the risk of standard medical care.

Epileptic seizures in this age group lead to high risk of neurodevelopmental compromise. Improved outcomes are achieved through seizure control. The risk of neurodevelopmental compromise has to be judged against any side effect of the KD and the latter minimised with diet manipulation. The duration of dietary treatment will therefore require continued evaluation at each visit of risk vs benefit of continuing for each individual.

The KD can cause side effects during application; most commonly these include constipation, diarrhoea and vomiting, which can usually be minimised by manipulation of the diet. Rarely, renal stones may occur. Regular blood evaluation is required to ensure no potential electrolyte imbalance or mineral deficiency. Clinical laboratory assessments for haematology, biochemistry, and ketone assessment in blood and urine have been designed into the trial as shown in Section 8.7. There will be metabolic screening prior to start of trial to check that there are no contraindications to use of the KD.

Expected Events with the Ketogenic Diet (Keene DL 2006, Neal et al, 2008)

Expected Event	Prevalence	Severity
Acidosis	Common	Mild
Change in lipids levels	Common	Mild
Constipation	Common	Moderate
Diarrhoea	Common	Moderate
Hunger	Common	Mild
Lethargy	Common (initial stage)	Mild
Pancreatitis	Rare	Severe

Renal stones	Occasional	Moderate
Vomiting	Common	Mild
Abdominal pain	Rare	Mild
Increase serum uric acid	Common	Mild
Hypoglycaemia	Occasional	Moderate

Additionally, although the KD is now frequently started on an outpatient basis in older children, the young age of many of the children recruited for this trial will mean that an inpatient admission is needed for initiation (the majority will already be inpatients for the management of their epilepsy owing to the frequency of seizures).

At each of the centres, the paediatric neurologist will work with the dietetic team using a manualised dietetic care pathway for KD implementation. Project management, data collection and analysis will be co-ordinated by a core team based at UCL, Great Ormond Street Hospital (GOSH) and the PRIMENT Clinical Trials Unit.

Full blood evaluation will involve blood draw of 2-3 mls of blood; anaesthetic spray will be used to numb the area before insertion of the needle.

The risk of blood tests are minimal:

- Sometimes a bruise develops where the needle was inserted. This is 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 is very rare and will be treated as per standard care.
- Rarely, some people feel faint during a blood test; this will be treated as per standard care

Children will be withdrawn from the treatment prior to 8 weeks should there be over 50% increase in seizure frequency from baseline, or if side effects, for example, diarrhoea or constipation, are not resolved by manipulation of KD or medication. Data from our previous RCT of the KD in 145 children aged 2-16 years(Neal *et al.*, 2008) showed 20% drop out before 3 months; we would expect this to be considerably lower in the younger children who would be less likely to have developed behavioural feeding problems.

If seizure control is not achieved on the KD arm by 8 weeks, those children will revert back to standard medical management.

Children on the AED arm will be prescribed further AEDs as per standard medical management. There is no additional risk to these children compared to standard care for the participation in the trial.

4 Objectives

OVERALL AIM: To determine the effectiveness on seizure control of the KD compared to alternative further AED treatment in children with epilepsy aged 1 month to 2 years who have failed to respond to two or more pharmacological treatments .

Hypotheses: The KD is more effective in reducing seizure frequency in infants (age 1 month to 2 years) with epilepsy who have failed to respond to 2 or more pharmacological agents (antiepileptic drugs or corticosteroids) compared to conventional management with an AED.

Primary aim: To determine the effectiveness of the KD on seizure frequency compared to alternative further AED treatment in children under 2 years with drug resistant epilepsy.

Secondary aims: To determine whether the presence of medium chain fatty acids in the context of use of the KD is associated with enhanced mitochondrial function and seizure control in children under two years of age.
To determine retention, quality of life and neurodevelopmental outcome at 12 months.

5 Trial design

5.1 Overall design

The project proposed is a non-commercial, open label randomised controlled multicentre clinical trial of children 1 month to 2 years of age with epilepsy who have failed to respond to two or more pharmacological treatments (AED or corticosteroids), comparing KD to further AED. The study will be conducted in two phases: first we will carry out a pilot phase in two centres. We will proceed to the full trial in a further 7 centres if we find the pilot is successful in terms of recruitment. The criteria for progression to the full trial are detailed in the analysis section. Further centres will be initiated in early 2017 to increase recruitment.

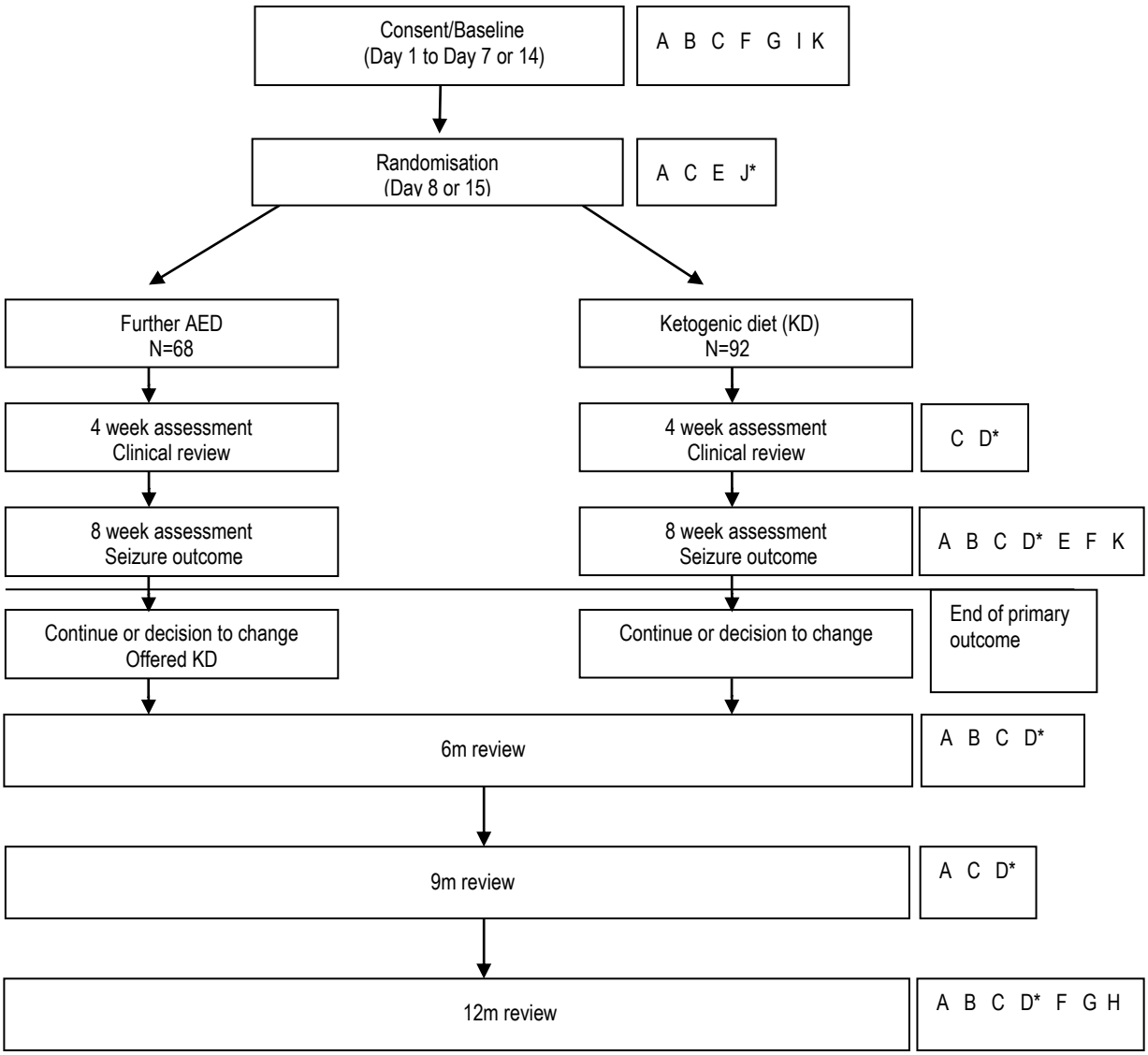
Eligible children will be consented via their parents to undergo baseline assessment, including medical and seizure history, neurological and anthropometric examination, administration of quality of life (Infant and Toddler Quality of Life Questionnaire, and developmental questionnaires (Vineland Adaptive Behaviour questionnaire, and biochemical investigations. They will then start a two week observation period with documentation of seizure frequency. However, if the child is prone to particularly frequent seizures in excess of 2/day then a minimum baseline period of one week would suffice. Food diaries required for diet calculation will be returned by post (or most practicable electronic means) from all enrolled infants one week (or sooner for those with an unstable clinical condition) into the observation period. Standardised seizure records will be kept during the observation period until 8 weeks thereafter, as stated in section 8.4. Randomisation will occur on Day 8 or Day 15 for them to receive the KD or a further AED; the allocated treatment will commence following randomisation, with instruction and training as necessary. A second assessment (4 weeks after start of treatment) will include

clinical review and questionnaire on tolerability (modified Hague scale of side effects). Assessments will be repeated at 8 weeks after the start of treatment, including clinical review, administration of the Infant and Toddler Quality of Life Questionnaire, the tolerability questionnaire, and biochemical investigations. After the 8-week assessment, according to patient's clinical response to treatment with regards seizure outcome and tolerability, the KD (diet group) or AED (standard AED group) will then be continued or changed. Those in the AED group who have failed to achieve seizure control at the 8 week assessment will then be offered KD outside the context of the trial, depending on KD waiting lists at the specific site – please note: a discussion should take place within the multidisciplinary team regarding dietetic availability prior to consent being taken. Those on the KD who have failed to achieve seizure improvement at the 8 week assessment will continue with medical management per clinician decision. All patients will be followed up for 12 months following randomisation for retention, seizure outcome and neurodevelopmental status.

At each of the centres, the paediatric neurologist will work with a dietitian using a manualised dietetic care pathway for KD implementation. Treatment will be in accordance with the 'KD intervention manual' will be agreed with reference to a standard text (Neal, 2012) and will be discussed with the project management team at the outset during the initial workshop to enable standardisation of treatment between the different centres. There will be an AED consensus flowchart (Appendix 2) for guidance regarding management of the participant's epilepsy, written following an initial workshop with paediatric neurologists from all nine centres.

Project management, data collection and analysis will be co-ordinated by a core team based at UCL Great Ormond Street Institute of Child Health, Great Ormond Street Hospital (GOSH) and PRIMENT Clinical Trials Unit.

Schematic of Trial Design



A	**Physical exam** (complete or symptom directed) including weight, length, head circumference, general examination
B	**Clinical Laboratory** - refer to section 8.8.1
C	Issue/collect seizure diaries
D*	Administer side effects questionnaire
E	Trial intervention. KD or further AED comparator group
F	Infant Toddler Quality of Life Questionnaire
G	Vineland Adaptive Behaviour Questionnaire
H	Seizure recording must be captured daily 28 days before 12 month review
I	Issue/collect food diary (baseline only)
J*	Home monitoring including urine dipstick and blood spot ketones
K	Special Assay or procedure. Blood Sample to be analysed by Simon Heales at ICH

*KD arm only

6 Selection of subjects

6.1 Inclusion criteria

1. Age between 1 month and 24 months of age (not beyond second birthday at baseline)
2. Diagnosis of epilepsy confirmed
3. Seizure frequency greater than or equal to 4 seizures/ week on average in the baseline period
4. Failed response to previous trial of two anti-epileptic drugs. In the case of infantile spasms this could include a trial of corticosteroids.
5. Children with written informed consent from parent/guardian

6.2 Exclusion criteria

1. Age <1m or > 24 months of age
2. No secure diagnosis of epilepsy
3. < 4 seizures/week on average in baseline period
4. Trial of < 2 AEDs
5. Continues on corticosteroids less than two weeks prior to randomisation
6. Metabolic disease contraindicating use of the KD e.g. pyruvate carboxylase deficiency, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency from previous medical investigation and screening at baseline.
7. Progressive neurological disease
8. Severe gastroesophageal reflux
9. Previous treatment with the KD
10. Concurrent participation in another clinical trial of an investigational medicinal product.
11. Patients who are prescribed investigational or unlicensed AEDs
12. Patients who have a listed contraindication as per the SmPC to any of the AEDs listed in the trial IMPs

7 Recruitment

Recruitment will be from hospital-based paediatric neurology centres implementing the KD. Many, if not all of the suitable patients will already be under the care of tertiary paediatric neurology centres according to National Guidelines (www.nice.org.uk/cg137).

Potential parents/guardians of participants will be contacted initially by a member of their direct healthcare team (who is also part of the research team at each site). Parents will be provided with the REC approved version of the Patient Information Sheet. Information containing the KIWE invitation letter and patient information sheet may be sent via post or electronically (eg. email). Participants are children. Consent will be obtained from the person with parental rights after they have read the information sheet and had their questions answered.

Participant Identification Centres (P.I.C sites) will also be used to help identify participants through patient records. These centres will provide information to the patient's parent/guardian in form of a patient information sheet and advise them to contact the clinical team directly should they wish to participate in the trial.

Methods used to ensure recruitment to the study: It is expected that all children with a diagnosis of epilepsy under the age of 2 years will be under review for management by tertiary paediatric services (www.nice.org.uk/cg137). Principal investigators in each centre will be responsible for individual unit awareness of the trial and consequent recruitment.

Deliverability
A feasibility survey suggests that approximately 40 eligible patients/year at GOSH and 10 patients/year at other centres. Assuming 70% recruitment, 84 patients will be recruited per year when all centres are open.

The initial pilot study will aim to recruit approximately 20% of the total sample required, i.e. 35 patients over 12 months. Thereafter should the outcome criteria of the pilot be met the trial will be open to the further 7 centres, and recruitment expected at a rate of 28/year from GOSH, and approximately 5/year from remaining centres (total 84/year). This enables a completed primary outcome in the desired 160 children.

Dietetic time has been allocated according to likely recruitment from each centre. All centres participating are tertiary paediatric neurology referral centres, and have existing KD services.

At present we are not aware of further studies that would be competing for recruitment. The International Collaborative Infantile Spasm Study (http://www.bath.ac.uk/health/research/iciss) is evaluating first line treatment (steroids vs vigabatrin with steroids) as initial treatment of infantile spasms and therefore is not competing for the same population. The proposed study would be an appropriate trial for those who continue to have seizures despite treatment with first line therapy.

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

Full ethical approval will be sought through an approved Research Ethics Committee prior to trial start. Standard Patient Information Sheets will be created and submitted for approval as part of this process.

Potential parents/guardians of participants will be approached initially by a member of their direct healthcare team (who is also part of the research team at each site), who will provide them with the REC approved version of the Patient Information Sheet.

Written informed consent will be obtained from each parent/guardian prior to participation in the trial, following a face to face or telephone consultation with an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Consent will be taken by the local site Principal Investigator (PI) (paediatric neurologist) or delegate who will be GCP trained and on the delegation log. If consent is obtained during a telephone consultation the site should note this on the consent form and consent must be confirmed by email or post with signature provided at the next face-to-face visit (ie.screening/baseline).
24 hours will be given for consideration by the parent/guardian before taking part with opportunity for the family to discuss any queries that have arisen. The PI must record when the patient information sheet (PIS) has been given to the patient. The PI or delegate will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the Investigator Site File and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

8.2 Randomisation procedures

The randomisation schedule will be independently generated and held by Sealed Envelope™ (Sealed Envelope Ltd.). Allocations will be released by email to the coordinating centres once the research nurse has entered eligible participant information into a web based randomisation service provided by Sealed Envelope

Participants will be allocated to either the KD or further AED arm using a simple randomisation method through consecutive allocation of subject numbers. As per Section 14.2, randomisation will be aimed to achieve 92 in the KD group vs 68 participants in the further AED arm. An Enrolment Log will be maintained at each site to keep records of the screened and randomised patients at site.

Withdrawn patients will not be replaced and replacement numbers will not be issued.

Randomisation will occur on Day 8 (if the child is prone to particularly frequent seizures in excess of 2/day) or Day 15 after the initial baseline visit. Whilst it will not be possible to blind participants to their treatment allocation, efforts will be made to minimise expectation bias by emphasising in the Patient Information Sheet that the evidence supporting the KD for seizure control is currently limited.

8.3 Screening Period

Potential participants will be identified at each site by the direct healthcare team. Parents of the eligible children will be consented prior to undertaking a baseline assessment. Full history including seizure type, neurological examination, weight, length and head circumference will be documented. Children requiring thickeners in their feed for reflux can be included in the trial as there is no interaction with the KD.

8.4 Baseline assessments

There will be an observation period of 2 weeks (or one week if the child is prone to particularly frequent seizures in excess of 2/day) during which there will be no changes of regular AEDs. Emergency seizure treatments will continue as required (acute treatment with benzodiazepines as per the patient's emergency protocol). The following data will be recorded in a standardised diary (these data will continue to be recorded throughout the intervention period of 8 weeks): seizure types, seizure frequency, number of emergency seizure treatments required, contacts with the NHS due to seizure exacerbation (hospital admissions - number of days, Accident & Emergency Unit and /or GP attendances). At the end of this period, randomisation to KD or standard AED group will be carried out on Day 8 or Day 15, as per section 8.2. Investigations to be performed in all children will include clinical laboratory assessments (refer to section 8.8.1), administration of the Infant Toddler Quality of Life Questionnaire (http://www.healthactchq.com/survey-itqol.php) and the Vineland Adaptive Behaviour (neurodevelopmental) questionnaire. Seizure diaries are to be kept daily from Baseline to Week 8. Thereafter, parents can reduce seizure recording to 1-2 days per week as clinically indicated. Seizure recording must then increase back to recording seizures daily 28 days before the final 12 month follow up visit; this is captured as part of the clinical evaluation at month 12. Seizure diaries may be provided to the parent/carer in person, by post or electronically and diary data may be collected electronically if needed (eg. by email). Questionnaire data may also be completed by remote methods (see Section 8.6)

8.5 Treatment procedures

Trial arm 1: Classical ketogenic diet (KD arm)

The experimental intervention will be an 8 week trial of KD therapy. A KD Intervention Manual (See Appendix 1) 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. In order to achieve a state of ketosis, meal plans have to be accurately calculated for each child individually and recorded in the patient's medical notes. Breast feeding can be continued on a KD, in combination with a ketogenic feed which will normally be given in a prescribed amount before each breastfeed. If breast milk is expressed, this can be mixed with the ketogenic feed to the correct macronutrient ratio. Infants on a KD can be weaned as per Department of Health guidelines, with advice given on how to adapt standard weaning foods by addition of extra fat.

Further adjustments to the KD are determined by regular growth monitoring (weekly weight checks are often performed as part of standard care, although this is not a requirement), seizure control and daily home measurement of urine or blood ketones. The latter will also indicate compliance with the dietary restrictions.

Hospital stays will be determined by the clinical team at the treating centre, utilising the KD Intervention Manual. A non-fasting initiation protocol will be used for all children. Parents or carers who will have a thorough teaching programme prior to diet commencement, including how to manage possible early side effects such as excess ketosis and hypoglycaemia. Teaching of families in the KD arm will occur on day 8 or 15 (as per the explanation provided in section 8.2) following randomisation.

The KD to be implemented will be the classical KD, aiming for at least a 3:1 (ratio of fat to carbohydrate and protein). An initial workshop of dietitians was led by Elizabeth Neal (Co-PI) in order to ensure consistency of implementation. All dietitians involved in KIWE are in regular contact with the Dietetic Assistant and a further dietitians meeting was organised to ensure continued cross-site consistency. Consistency of KD implementation will be monitored after the 8-week and 12-month visits by the Dietetic Assistant. Details to be monitored include the calculation of energy prescriptions, protein intake, teaching sessions, initiation regimes, supplementation and ketone levels. Monitoring discrepancy forms will be created and the protocol deviation log completed, if appropriate.

Trial arm 2: Further Anti-epileptic drugs (AED arm)
The control intervention will be drug therapy with the 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 the 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.
Paediatric neurologists will meet at the initial workshop and discuss practice, utilising guidelines and this will form the basis of a consensus document to ensure consistency of treatments delivered.

A discussion about diet will be undertaken with families of infants randomised to the AED arm at the randomisation visit. If the participant is already under local dietetic support, it should be ensured that this monitoring continues. If the participant does not have local dietetic support but this is deemed necessary by the ketogenic dietitian, an appropriate referral should be made by the clinician. A very brief discussion about general infant or toddler nutrition will be had, including details such as promotion of breastfeeding, age-

appropriate texture progression for weaning, food groups and the important of iron-rich foods.

8.6 Subsequent assessments

NOTE: Due to the COVID-19 pandemic visits (during and subsequently) may be conducted remotely by telephone or secure videoconference facility if the parent/carer does not wish to travel and/or bring the child into the hospital or there are concerns around safety. In all cases this is up to the discretion of the treating consultant and the parent/carer will be advised by the local KIWE team. Remote methods may also be employed for the issuing and collection of diary data or the completion of questionnaires. Existing samples may also be used for screening but only if blood is no older than 6 weeks or blood tests may be carried out locally (eg at a GP surgery or hospital local to the child).

Start of the Classical KD (diet group) or new AED: The recording of seizure types and frequency is to be continued. Commencement of daily monitoring of urine ketone levels by the parents or carers of children in the KD group (this monitoring to continue throughout the trial period on which the children are on the KD diet).

Second Assessment (4 weeks after start of treatment period, all patients): clinical review can be completed over the telephone if appropriate, including weight; documentation of seizure frequency (from seizure diaries), and administration of the side effect questionnaire. Review of adverse events and concomitant medication. Compliance with KD intervention manual and protocol will be reviewed by the Dietetic Assistant.

Third assessment (8 weeks after starting treatment/ all patients): Clinical review including a symptom directed physical examination, weight, length and head circumference, and documentation of seizure frequency (from seizure diaries). Completion of side effect/tolerability questionnaire, clinical laboratory assessments (refer to section 8.8.1) .and the administration of the Infant Toddler Quality of Life Questionnaire (KINDL)(http://www.healthactchq.com/survey-itqol.php).

Assessment at 6 and 9 months: Clinical review including a symptom directed physical examination, weight, length and head circumference, and documentation of seizure frequency (from seizure diaries). Completion of side effect/tolerability questionnaire and clinical laboratory assessments (refer to section 8.8.1) at month 6 only.

Final assessment (12 months after start of treatment period, all patients): This will include clinical evaluation of seizure frequency (seizure diaries maintained and seizure frequency taken as an average daily frequency over the 28 days prior to review), medications, quality of life questionnaire, Vineland adaptive questionnaire, complete physical examination, review of adverse events and clinical laboratory assessments (refer to section 8.8.1). Compliance with KD intervention manual and protocol will be reviewed by the Dietetic Assistant.

Participants who are withdrawn during the trial will complete the 12 month follow up assessments.

8.7 Flowchart of study assessments

Visit Number		1	2	3	4	5	6	7	8
Time point		Screening	Baseline[1] Day 1 to Day 14	Randomisation Day 15	4 weeks	8 weeks	Month 6	Month 9	Month 12
Allowed deviation window		N/A	+/-2 days	+/-7 days			+/- 1 month		
Informed Consent		X							
Assessment of Eligibility Criteria		X		X					
Review of Medical History		X							
Review of Concomitant Medications			X	X	X	X	X	X	X
Assessment of Adverse Events				X	X	X	X	X	X
Trial Intervention – ketogenic diet **			X	X	X	X			
Physical Exam	Complete [1]	X							X
	Symptom-Directed		X	(X)	(X)	(X)	(X)	(X)	(X)
	Vital Signs		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Clinical Laboratory[2]	Haematology		X			X**	X**		X**
	Biochemistry		X			X**	X**		X**
	Urinalysis		X			X**	X**		X**
Home monitoring**	Urine dipstick + Blood spot ketones [3]			X**	X**	X**			
Special Assay or Procedure[4]	Fatty acids (blood sample to Simon Heales at ICH)		X			X			
Comparator group (Further AED treatment relevant to trial)				X	X	X			
Quality of Life (KINDL)			X			X			X
Seizure Diary Data (to be entered in eCRFs through discussion with patient and review of their seizure diary)			X	X	X	X	X	X	X

Visit Number	1	2	3	4	5	6	7	8
Time point	Screening	Baseline[1] Day 1 to Day 14	Randomisation Day 15	4 weeks	8 weeks	Month 6	Month 9	Month 12
Allowed deviation window	N/A	+/-2 days	+/-7 days			+/- 1 month		
Neuropsychological Assessment (Vineland)		X						X
KD Side effects questionnaire**				X**	X**	X**	X**	X**
KD Food diary		X						

*At baseline, all procedures should be done before randomisation
**Ketogenic diet group only
(X) – As indicated/appropriate
[1] Complete physical includes weight, length, head circumference, general examination
[2]Haematology, biochemistry and urinalysis (refer to section 8.8.1)
[3] Home monitoring urine dipstick and blood spot ketones done twice a day (optional) and recorded in Seizure diary (only KD arm)
Urinalysis – organic acids
[4]Special assay or procedure – Blood sample to be analysed by Simon Heales at ICH.

8.8 Methods

8.8.1 Laboratory procedures

Clinical laboratory investigations taken at baseline, week 8, month 6 and month 12 are:

FBC [white blood cell, platelets, haemoglobin]

U&Es [urea, sodium, potassium, chloride, bicarbonate, creatinine]

LFTs [total protein, bilirubin, albumin, alkaline phosphatate, alanine transaminase, aspartate transaminase]

Glucose

Calcium

Phosphate

Vitamin D

Selenium

Zinc

Magnesium

Cholesterol

Triglycerides

Acylcarnitine profile

Non-esterified fatty acids (NEFA),

Beta-hydroxybutyrate (BHB – to be taken at baseline and week 8 only)

Urine calcium/creatinine ratio

Urine organic acids

The special assay is to be taken at baseline and 8 weeks only. This is to be taken from patients on the KD arm and AED arm.

Results must be received prior to randomisation except for the special assay which will be processed at the Chemical Pathology Laboratory at GOSH.

The blood and urine samples for the secondary outcome will be processed at local labs. The special assay blood samples to evaluate the plasma profiles of medium chain fatty acids and for the assessment of mitochondrial function (respiratory chain enzymes) and enrichment (citrate synthase) will be processed at the Chemical Pathology Laboratory at GOSH. A sample management SOP has been created to outline the details of sample collection and shipment to the central laboratory from local sites.

NOTE:

- If the central laboratory at GOSH is unable to accept samples due to a pandemic or similar situation then samples should be stored locally where possible in a secure place. The team should ensure that the samples are stored with the correct label (detailing patient trial/screening ID) and form which should be enclosed with the sample when it is couriered to the central laboratory at a later date. The label and form can be provided by the Trial Manager.
- When the central laboratory can accept samples please follow the courier instructions detailed in the sample management SOP.
- If the local laboratory is unable to accept samples above standard of care the Trial Manager must be informed.

Urine (via dipstick) or blood (via blood spot) ketones, dependent on parental preference, will be monitored at home twice daily whilst a child on the KD. Full instructions will be given to parents on the procedure involved at the time of KD training.

8.9 Definition of end of trial

End of trial will be 12 months following recruitment of last patient i.e. last visit of last patient for 12 months review.

8.10 Discontinuation/withdrawal of participants and ‘stopping rules’

Participants will be withdrawn from the treatment prior to 8 weeks should there be over 50% increase in seizure frequency from baseline, or if side effects e.g. diarrhoea or constipation, are not resolved by manipulation of KD or medication.

Withdrawn patients will not be replaced, but will have 12 month follow up assessment.

9 Name and description of all drugs used in the trial

The trial will compare the efficacy of the KD to a further appropriate AED when a child has failed 2 AEDs. The AEDs to be used are Carbamazepine, Clobazam, Clonazepam, Ethosuximide, Lacosmide, Lamotrigine, Levetiracetam, Nitrazepam, Phenytoin, Sodium Valproate, Stiripentol, Topiramate, Vigabatrin, Zonisamide and Rufinamide.

9.1 Treatment of subjects

Investigational product/treatment

The experimental intervention will be an 8 week trial of KD therapy. KD is not classed as a medicinal product.

The control intervention will be drug therapy with the most appropriate further AED for a particular child as per standard clinical decision (see below).

9.2 Concomitant medication

All concomitant medication will be recorded. All medications such as antibiotics or painkillers should be carbohydrate-free. Intravenous (IV) dextrose infusions should be avoided if possible, although a small amount of glucose may be needed to maintain blood glucose levels if continued IV support is necessary. Blood glucose should always be closely monitored. Medications contraindicated with any of the listed IMPs should be avoided.

10 Investigational Medicinal Product

10.1 Name and description of investigational medicinal product(s)

Products listed in the table below are considered as investigational medicinal products (IMPs) in this trial, irrespective of which arm of the trial the patient is randomised to. This is a pragmatic trial that uses authorised medicinal products for epilepsy within the EEA. Although the majority of these IMPs are not licenced for paediatric use or for use in this age group, these drugs are used in routine care as part of established clinical practice. Patients who are prescribed products with no marketing authorisation (e.g.“specials”) for epilepsy or AEDs not listed in the below table will not be eligible for this trial.

KD is not classed as a medicinal product and is not included in this table.

Medicines	Formulation	Concentration
Carbamazepine (Tegratol)	Liquid	100mg/5mL
	Tablets	100, 200, 400mg
Clobazam (Frisium)	Oral suspension	5mg/5mL
		10mg/5mL
	Tablets	10mg
Clonazepam (Rivotril)	Oral solution	0.5mg/5mL
		2mg/5mL
	Oral drops	2.5mg/mL
	Tablets	500 micrograms, 2mg
Ethosuximide (Zarontin)	Syrup	250mg/5mL
	Capsules	250mg
Lacosmide (Vimpat)	Syrup	10mg/mL
	Tablets	50, 100, 150, 200mg
Lamotrigine (Lamictal)	Dispersible tablets	2mg
		5mg
		25mg
		100mg
Levetiracetam (Keppra)	Oral solution	100mg/mL
	Tablets	250, 500, 750, 1000mg,
Nitrazepam (Mogadon)	Oral suspension	2.5mg/5mL
	Tablets	5mg
Phenytoin (Epanutin)	Suspension	30mg/5mL
	Infatabs	50mg
	Capsules	25, 50, 100mg
Rufinamide (Inovelon)	Tablets	100, 200, 400mg
	Oral suspension	40mg/mL
Sodium Valproate (Epilim)	Oral solution	200mg/5mL
Stiripentol (Diacomit)	Powder (sachets)	250mg
		500mg
	Capsules	250mg, 500mg
Topiramate (Topamax)	Sprinkle capsules	15mg
		25mg
		50mg
	Tablets	25mg
		50mg
		100mg
Vigabatrin (Sabril)	Powder (Sachets)	500mg
Zonisamide (Zonegran)	Capsules	25mg
		50mg
		100mg

10.2 Name and description of each NIMP

There are no NIMPs in this trial. Children in the KD arm who fail to achieve seizure control after 8 weeks will revert back to standard medical management, including the use of routine anti-epileptic drugs.

10.3 Summary of findings from non-clinical studies

There are no non-clinical studies done that are relevant to this trial.

10.4 Summary of findings from clinical studies

Please refer to Section 3.2.

10.5 Summary of known and potential risks and benefits

Please refer to Section 3.3.

10.6 Dosages, dosage modifications and method of administration

Clinicians should tailor the dosage of IMPs for each individual patient according to their usual practice. See Section 10.1 for more information.

10.7 Preparation and labelling of Investigational Medicinal Product

Regulation 46(2) of SI 2004/1031 will be applied to this trial.
All treatment should be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 as that apply in relation to dispensed relevant medicinal products.
All IMPs should be stored as per normal clinical practice in accordance to the Summary of Product Characteristics.

10.8 Drug accountability

There are no formal accountability measures required for the trial, as AED treatments will be prescribed according to the local medical practices and dispensed by hospital and community pharmacies as they would be normally in clinical practice. The further AEDs prescribed after randomisation on the AED arm will be recorded in the CRF. Changes in the AED treatment during the 8 weeks will be captured with the use of the seizure diary.

10.9 Source of IMPs including placebo

All IMPs will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the Pharmacy. There is no placebo in this trial. The IMPs should be prescribed and issued as per routine practice, in accordance with a prescription given by an authorised health care professional.

Investigators should only prescribe formulations listed in the table above, which are authorised products within the EEA. There will be no modifications made to the products or their outer packaging.

The products can be dispensed from the general pharmacy stock, either by hospital or community pharmacies as they would be normally in clinical practice. It is the responsibility of the investigator to ensure that the GP is prepared to prescribe the remainder of any trial treatment not dispensed by the hospital pharmacy.

10.10 Dose modifications

Not applicable. Dosages in the further AED arm will be prescribed as per routine clinical management.

10.11 Assessment of compliance

Compliance includes both adherences to IMP and Protocol study procedures. Treatment compliance will be captured with the use of seizure diary and food diary.

Noncompliance to the Protocol study procedures will be documented by the investigator and reported to the Sponsor as agreed. Persistent noncompliance may lead the patient to be withdrawn from the study.

Efficacy of the KD and further AEDs will be assessed through documentation of seizure frequency by seizure diaries completed by parents throughout, with documentation to CRF at each assessment.

10.12 Post-trial IMP arrangements

There are no post trial IMP arrangements. After 8 weeks, if seizure control is not achieved, local decision can be made to continue or change from KD or further AED in both arms as vice versa.

Patients will be followed up for 12 months and it would be anticipated that clinical data would be collected on all patients at 12 months to determine outcome and retention rates.

11 Recording and reporting of adverse events and reactions

11.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

11.2 Recording adverse events

All adverse events will be recorded in the medical records and CRF following randomisation (Day 15), apart from parent-reported seizures which will be recorded in the seizure diary. Ongoing seizures are an expected adverse event in this population and only seizures that meet the seriousness criteria will be entered on the CRF AE log (see section 11.4). The AE log will be reviewed at the TMG meetings although immediate review (within 24 hours) of SAEs will be performed by the CI/PI.

If the investigator suspects that the subjects' condition has progressed faster due to the administration of the IMP, then they will record and report this as an unexpected adverse event.

Clinically significant abnormalities in the results of objective tests (e.g. laboratory variables, EEG) will also be recorded as adverse events. If the results are not expected as part of disease or IMP, these will also be recorded as unexpected.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be reportable to PRIMENT up to 30 days post last IMP administration.

11.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

11.3.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

11.3.2 Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

11.3.3 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

The reference document to be used to assess expectedness against the IMPs are the Summary of Product Characteristics (SMPCs) for the brands listed in table 10.1 The expected AEs for the KD are detailed in Section 3.3

Expected Epilepsy AEs:

- The possible epilepsy adverse event in this trial would be the occurrence of status epilepticus requiring hospitalisation or prolongation of existing hospital stay.
- Injury sustained from epilepsy which could require hospitalisation.

11.3.4 Seriousness

Seriousness as defined for an SAE in section 11.1.

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the PRIMENT SOP Investigator Pharmacovigilance.

11.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the hospital notes and the CRF, and the sponsor's AE log from randomisation until last visit. The AE log will be reported to the sponsor at least once per year.

The Chief or Principal Investigator will complete the sponsor's serious adverse event form (if reportable – see SAE reporting criteria section 11.4.1) and the form will be emailed to PRIMENT on PRIMENTsafetyreport@ucl.ac.uk, within 24 hours of her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by PRIMENT as soon as possible.

All SUSARs must be notified to PRIMENT immediately (within 24 hours) according to PRIMENT's written SOP.

Reporting to the sponsor will be completed as per PRIMENT's SOP and using the KIWE SAE form.

11.4.1 SAE reporting criteria:

- Expected epilepsy adverse events as listed in section 11.3.3 will not be reportable to the Sponsor unless the CI/PI assess the event as more severe than expected.
- For patients on the AED arm, SAEs will not be reportable to the Sponsor as the IMPs are well established drugs used within their licensed indication.
- For patients on the KD arm, all SAEs will be reportable to the Sponsor, unless expected for epilepsy

All the above SAEs will be reviewed by the TMG at their regular meetings. All SARs will be reportable to PRIMENT within 24 hours.

11.4.2 Notification of deaths

Only deaths that are assessed to be caused by the IMP will be reported to PRIMENT. This report will be immediate.

11.4.3 Reporting SUSARs

PRIMENT will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after PRIMENT has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after PRIMENT has learned of them.

The TM will be responsible for the dissemination of SUSARs to all sites. These will also be discussed in the TMG.

11.4.4 Development Safety Update Reports

PRIMENT will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and PRIMENT. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

11.4.5 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

11.4.6 Overdose

Overdose of the KD is not possible. Overdose on the further AED arm is not envisaged as these drugs are prescribed as per routine care with instructions to parents. Overdoses will be managed as per routine standard care. All overdoses will be noted in the medical records, CRF and if associated with an SAE will be reported to PRIMENT using the KIWE SAE report form.

11.4.7 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/PRIMENT shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

11.5 The type and duration of the follow-up of subjects after adverse events

Any SUSAR related to the IMP will need to be reported to PRIMENT irrespective of how long after IMP administration the reaction has occurred.

11.5.1 Notification of Serious Breaches to GCP and/or the protocol (SPON/S15)

A “serious breach” is a breach which is likely to effect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.
The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –
(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.
PRIMENT will be notified immediately of any case where the above definition applies during the trial conduct phase. PRIMENT SOP serious breached of GCP or trial protocol will be followed.

12 Data management and quality assurance

12.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.
The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

12.2 Data collection tools and source document identification

The investigator will ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Whilst inpatient and at each outpatient visit, medical notes will form the source data for the trial and be completed as per routine practice.

A Source Document List will be completed for the trial prior to trial start.

12.3 Data handling and analysis

The Trial Manager will conduct day-to-day central monitoring of the study. The trial manager will work closely with PRIMENT to ensure feasibility of data collection and the design of CRFs. The data handling standard operating procedures (SOPs) provide clear guidance on data monitoring checks and handling errors. Site nurses at each participating centre will receive standardised training in data collection procedures. Data entry at participating centres will be done electronically on web based systems provided by Sealed Envelope and designed with advice from PRIMENT. The system is GCP compliant and access will be restricted to trained and authorised individuals. It will include built in range and consistency checks designed to minimise data entry errors and an audit trail to log changes to data.

Data collected on paper source data such as seizure diary, food diary etc at various sites is sent to the coordinating centre for data entry; conducted by experienced staff employed on the study. These data are subjected to range and consistency checks and any queries so identified are checked against the paper records or with the relevant participating centre. There are standard existing procedures for checking discordant data on paper records with each of the participating centres if necessary.
All paper source data are kept in a secure area at the coordinating centre during the course of the study and then stored by the chief investigator for 20 years.

If any data problems are identified, a data clarification form will be sent to the centre by post or email for checking and confirmation or correction. Any data which are changed on the paper source data will be crossed through with a single line so as not to prevent reading the original and initialled and dated on the site copy of the CRF. The coordinating centre will send reminders for any overdue and missing data.

PRIMENT will also monitor centres for data compliance in terms of data quality and CRF return.

13 Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report.

Chief Investigators are responsible for the secure archiving of essential trial documents (for each site, if multi-site trial) and the trial database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the Sponsor.

14 Statistical Considerations

Professor Nicholas Freemantle is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

1. The pilot study will run in two centres in London; Great Ormond Street Hospital for Children and the Evelina Children's Hospital in London over the initial 12 months. We will assess approximately 50 eligible patients in this time frame. Additionally adverse events will be monitored; and data on safety will be reviewed. We will progress to the full study if the following are achieved

a. Achieving a 60% recruitment rate; i.e. 30 families agreeing to randomisation

b. No more than 10 (29%) failing to complete the 8 week trial period.

2. The main study will proceed to include recruitment from the further 7 centres should the above criteria be met.

Baseline characteristics of participants in the control and intervention arms will be summarised. Frequencies and measures of central tendency will be calculated by randomised group to check for differences in the data. The primary outcome will be seizure count in the final two weeks of the intervention period and in the baseline assessment period. Data will be analysed using a Poisson mixed model to account for clustering by centre (synonymous with therapist). The randomised allocation will be entered into the model as a fixed effect as will an indicator of time point (baseline or end of study), whilst the centre will be included as a random effect. Analysis of secondary outcomes (those seizure free and responders) will be analysed using random effects logistic models; centre being the random effect and randomised group a fixed effect. The process outcomes relating to tolerability and medium chain fatty acids in the KD group will be analysed using random effects modelling. Therapist effects will be investigated further in supportive analyses (Agresti and Hartzel, 2000).

14.1 Outcomes

14.1.1 Primary outcomes

The primary outcome will be the number of seizures recorded during weeks 6-8 compared to the number of seizures recorded in the baseline period.

14.1.2 Secondary outcomes

Secondary outcomes will include (at 8 weeks):

- number of children seizure free
- responder rate, defined as the number showing more than a 50% in improvement in seizure frequency compared to baseline (taken as the mean daily seizure frequency over the two week period immediately preceding the 8 week review)
- tolerance to KD as assessed by questionnaire and blood results
- relationship between medium chain fatty acids and seizure control

Secondary outcomes will also include (at 12 months):

- retention on treatment
- quality of life (as measured by the Infant Toddler Quality of Life Questionnaire neurodevelopmental outcome (as measured by Vineland Adaptive Behaviour Scales)

Plasma profiles of medium chain fatty acids will be evaluated at baseline and at 8 weeks. Assessment of mitochondrial function (respiratory chain enzymes) and enrichment (citrate synthase) will be determined in white cells and platelets. The effect of specific ratios of medium chain fatty acids, to mimic patient plasma profiles, upon neuronal mitochondrial function/enrichment (biochemical plus electron microscopy studies) will be documented. Additionally, such fatty acid profiles will be studied, with regards to anti-epileptic effect, in an established in vitro (hippocampal slice) model.

14.2 Sample size and recruitment

14.2.1 Sample size calculation

For the primary outcome variable, based on data from Neal *et al.* (2008), we used mean percentage change in seizures from baseline of 62% (SD 45) in the diet group, assuming a change of 90% in the comparison group (SD 50) (100=no change in frequency of seizures from baseline) at 90% power and 5% significance. This gives a sample size of 61 in each group (122 in total); accounting for a 10% drop out rate gives 68 in each group (136 in total), and inflation for a therapist effect (dietitian) to one group, assuming 9 centres, with an average cluster size of 8 and an intraclass correlation coefficient of 0.05, the inflation factor is 1.35, giving 92 in the KD group and 68 in the control group (160 in total). If drop out was 20%, this sample size would still have 86% power.

14.2.2 Planned recruitment rate

See Section 7.0.

14.3 Statistical analysis plan

Analysis will be done on an intention-to-treat model. A full statistical analysis plan will be created by PRIMENT.

The pilot study will run in two centres in London; Great Ormond Street Hospital for Children and the Evelina Children's Hospital in London over the initial 12 months. We will assess approximately 50 eligible patients in this time frame. Additionally adverse events will be monitored; and data on safety will be reviewed. We will progress to the full study if the following are achieved:

a. achieving a 60% recruitment rate; i.e. 30 families agreeing to randomisation.

b. No more than 10 (29%) failing to complete the 8 week trial period.

The main study will proceed to include recruitment from the further 7 centres should the above criteria be met.

Baseline characteristics of participants in the control and intervention arms will be summarised. Frequencies and measures of central tendency will be calculated by randomised group to check for differences in the data.

14.3.1 Primary outcome analysis

The primary outcome will be seizure count in the weeks 6 to 8 of the intervention period and in the baseline assessment period. Data will be analysed using a Poisson mixed model to account for clustering by centre (synonymous with therapist). The randomised allocation will be entered into the model as a fixed effect as will an indicator of time point (baseline or end of study), whilst the centre will be included as a random effect.

14.3.2 Secondary outcome analysis

Analysis of secondary outcomes (those seizure free and responders) will be analysed using random effects logistic models; centre being the random effect and randomised group a fixed effect. The process outcomes relating to tolerability and medium chain fatty acids in the KD group will be analysed using random effects modelling. Therapist effects will be investigated further in supportive analyses (Agresti and Hartzel, 2000).

14.4 Randomisation methods

The randomisation schedule will be generated by computer. A simple randomisation method is used with no stratification by centre (to avoid potential allocation bias in an open study). The randomisation schedule will be independently generated by PRIMENT and allocations released by e-mail to the coordinating centres once the research nurse has entered participant information onto an online randomisation website. This will conceal allocation to treatment from the research nurses. Randomisation will occur on Day 15 after the initial baseline visit. Whilst it will not be possible to blind participants to their treatment allocation, efforts will be made to minimise expectation bias by emphasising in the trial literature that the evidence supporting the KD for seizure control is currently limited.

15 Name of Committees involved in trial

The study will be supported by the UCL PRIMENT CTU. The Chief Investigator (CI) will maintain day to day responsibility for the trial working in close collaboration with the Clinical Trial Manager (CTM) to ensure that the trial is conducted, recorded and reported in accordance with the protocol, good clinical practice guidelines, and essential standard operating procedures on all aspects of trial management, quality control and data analyses required for running RCTs as documented by our Clinical Trials Unit. All investigators will have up to date Good Clinical Practice training.

A Trial Management Group (TMG) consisting of the CI, some of the co-applicants the CTM and the trial statistician will meet monthly at the start of the study and then quarterly on completion of recruitment. They will monitor the conduct and progress of the trial. The PI, CTM and statistician will monitor data to identify unusual patterns (Central Monitoring Processes). They will also ensure that the researchers have access to documentation necessary for the conduct of the trial.

The study will be overseen by an externally led Trials Steering Group (TSG) that will meet twice a year which will include two parent representatives recruited from Young Epilepsy.

We will also appoint a trial data monitoring committee (DMC) that will examine baseline data and then explore the preliminary analyses of study outcomes and adverse events conducted on the data at defined time points as determined by the Chair of the DMC. Based on predefined cut off agreed by the DMC for specified outcomes the DMC will advise the TSG on the progress of the trials.

Terms of Reference will be in place for each committee.

16 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation. Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 0 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

18 Monitoring requirement for the trial

A trial specific monitoring plan will be established for this trial in line with Sponsor SOPs. The trial will be monitored with the agreed plan.

Training of researchers and collection of data: An initial workshop is proposed to include all dietitians and paediatric neurologists included in the study. It would also include the

involvement of Matthews Friends and parents named as collaborators. The purpose of this workshop would be:

For clinicians involved to discuss AED protocols and agree as far as is possible care pathways and AEDs of choice for each type of epilepsy, as well as adverse event reporting.

Dietitians to discuss classical KD protocols and standardise where possible, e.g. initiation, how quickly ratios obtained, fine tuning options, adverse event reporting, use of specific KD products (e.g. Ketocal), cows' milk intolerance, breast feeding, weaning, tube feeding and ketone monitoring.

Regular meetings of research teams are proposed x2/year. These initial consultations will determine the detail of the intervention which will be specified in a treatment manual which will be used at each centre to standardise the delivery of the treatments in the intervention and treatment group.

Consistency between centres will be ensured by utilisation of a Dietetic Assistant who will monitor (either face to face or remotely)each centre on a number of occasions during the course of the study to verify standard implementation of the diet and AED use as per the treatment manual written at the outset of the study.

19 Finance

The trial is being financed by an NIHR EME programme grant until 30th June 2021

20 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

21 Publication policy

All proposed publications will be discussed with Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to UCL publication policy.

22 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

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Appendix 1 KD intervention manual

Version 3.0 dated 14/04/2016

1. SUMMARY OF DIET IMPLEMENTATION

- Infants will be initiated on the classical ketogenic diet (KD).
- This will usually be started at a 2:1 ratio and increased to a 3:1 ratio (or 4:1 ratio) as tolerated; younger infants under 12 months old may be initiated in hospital.
- Blood ketone levels of at least 2mmol/l will be aimed for. Ideal therapeutic levels are usually over 4mmol/l but this will depend on an individual's seizure control and tolerance to ketosis.
- Blood glucose should be monitored during initiation.
- Breast feeding can be incorporated into a KD in conjunction with a ketogenic formula where possible if this is the parent's preference. Standard weaning guidelines should be followed.

2. CALCULATON OF CLASSICAL KD

Energy prescription
Energy intake is carefully controlled on the classical KD. The energy prescription (calories) should be sufficient to allow for normal growth and development however excess dietary energy and weight gain will cause poor ketosis which can in turn compromise potential seizure control. An energy prescription should always be individually calculated, taking into account the following:

a. Age
b. Current weight and length and recent growth trends
c. Individual pre-KD energy intake, assessed by a food/feed record diary for 3 or 4 days
d. Medication use
e. Energy expenditure based on mobility, level of physical activity, and seizure activity
f. UK recommendations for energy requirements/intakes for infants of different ages (Scientific Advisory Committee on Nutrition, 2011).

An initial dietary energy prescription must be closely monitored and adjusted as needed, especially during the first few weeks and months of treatment. If the prescribed energy intake does not maintain growth it must be increased, and likewise if weight gain is excessive it will lead to poor ketosis and energy will need to be reduced. Dietary energy increases and decreases should always be done in controlled increments.

Protein intake
Guidelines for 0-2 year olds suggest a prescription of 1.1-2.6g/kg/day: the UK recommended nutrient intake (RNI) for protein according to age (taken from Great Ormond Street Nutritional Requirements booklet 2014). In practice, this may not be achievable and so the protein prescription may be set somewhere between the World Health Organisation (WHO) recommendations for ‘safe’ levels of protein intake and the RNI. WHO recommendations for 'safe' levels of protein intake in infants are 1.36g/kg body weight at 3 months of age, 1.24g/kg at 4 months of age, 1.14g/kg body weight at 6 and 12 months of age, 1.03g/kg at 18 months of age and 0.97g/kg at 2 years of age (taken from WHO technical report No. 935 (World Health Organisation, 2007). The amount of protein allowed in a classical KD prescription will usually include that provided from all types of

food but protein quality must also be considered due to the importance of meeting requirements of all indispensable amino acids. The allowed amount of protein will be in many cases be only just above the recommended safe levels, so high biological value sources (e.g. meat, fish, eggs, dairy products) should be chosen wherever possible. If these foods are not routinely used in the diet, this must be taken into account and the prescription adjusted to allow more protein.

Diet ratio

The classical KD is calculated using the original ratio method (Talbot, 1930). A ketogenic ratio tells us the proportion (in grams) of fat in the diet as compared with carbohydrate and protein, e.g. a typical 4:1 ratio refers to a diet with a ratio of 4g of fat to 1g of protein plus carbohydrate combined. Most infants on classical KDs will start at 2:1 ratio, with a likely increase of up to 3:1 however some require higher to achieve the necessary seizure control. Some children with very low energy requirements may not meet their safe protein requirements on a 4:1 ratio. For these children it may be necessary to add extra protein to feeds or meals to meet safe protein levels and hence it may be difficult to achieve a 4:1 ratio. **Table 1** gives more detail on KD ratios.

Table 1. Explanation of the ratio system used to calculate the classical KD (taken from Magrath and Neal, 2012)

Diet ratio	Macronutrient proportions		Percentage of dietary energy from macronutrients	
	Fat (grams)	Protein and carbohydrate combined (grams)	Fat (%)	Protein and carbohydrate combined (%)
1:1	1	1	69	31
2:1	2	1	82	18
3:1	3	1	87	13
4:1	4	1	90	10

Diet prescription

Once the required energy, protein and ketogenic ratio have been determined, the rest of the prescription can be calculated to give the prescribed daily amounts of fat, protein and carbohydrate. The easiest method is by using dietary units; a unit is calculated from the calorie content of each of the macronutrients in the chosen diet ratio, based on fat providing 9 kcals per gram and protein and carbohydrate providing 4 kcals per gram each. This is based on a method described in more detail by authors from Johns Hopkins Hospital, USA (Kossoff et al., 2011), and shown below for the 4:1, 3:1 and 2:1 ratios:

Ratio 4:1: Each dietary unit = 4g fat and 1g protein and carbohydrate.
Energy content of each dietary unit = (4 x 9 kcals) + (1 x 4 kcals) = 40 kcals.
Ratio 3:1: Each dietary unit = 3g fat and 1g protein and carbohydrate.
Energy content of each dietary unit = (3 x 9 kcals) + (1 x 4 kcals) = 31 kcals.
Ratio 2:1: Each dietary unit = 2g fat and 1g protein and carbohydrate.
Energy content of each dietary unit = (2 x 9 kcals) + (1 x 4 kcals) = 22 kcals.

The total daily dietary energy allowance is divided by the kcals per dietary unit (this will depend on which ratio is to be chosen. This number is then multiplied by the units of fat in the ratio to give the total daily allowance of fat. The unit of carbohydrate and protein combined in the ratio is one; this is multiplied by the number of allowed daily dietary units to give the total daily amount of both macronutrients together. The protein allowance has already been determined; this can be subtracted to give the carbohydrate allowance.

3. DIET IMPLEMENTATION

Fluid
Normal fluid requirements should be maintained with no fluid restriction.

Food and feeds
Once total daily amounts of fat, protein and carbohydrate are calculated they can be divided up over the day in feeds or meals and snacks as required, all keeping to the same ketogenic ratio. If using meals and snacks, these can be calculated using recipes or exchange lists, depending on the practice implemented by the hospital centre.

The classical KD can be given as a complete or part liquid feed, either taken orally (e.g. for young infants) or given enterally, using a ketogenic formula such as KetoCal (Nutricia: available as 3:1 and 4:1 ratio powders and 4:1 ratio liquid feed). This may need adjusting with an added carbohydrate module to the appropriate ketogenic prescription. If an infant is using this as a complete feed, extra supplemented micronutrients are not usually necessary but this should be checked against requirements. However KetoCal 4:1 (powder or liquid) does not meet recommended guidelines for nutritional content of infant formulae so is not suitable as a sole source of nutrition without careful consideration of individual nutrients. In particular the sodium content of KetoCal 4:1 is higher than that of normal infant formulae; potassium content is also higher and the calcium:phosphate ratio is too low (Dos Santos, 2012).

If an infant is being breastfed, this can be continued at a lower volume, with a prescribed amount of KetoCal given before each feed based on the theoretical fluid and dietary energy intake for age. This will limit intake of breast milk and thus maintain a ketogenic ratio. If breastmilk is expressed, this can be mixed with KetoCal, ensuring each bottle contains the combination feed in the correct ratio (Dos Santos, 2012).

Feed thickeners can be used if required but the carbohydrate content should be considered.

Infants should be weaned as per Department of Health (DOH) and British Dietetic Association guidelines (DOH, 200; British Dietetic Association, 2010). Nutritional requirements should be assessed and supplementary micronutrients may be needed at this stage. Foods which are good sources of vitamin C should be encouraged in the weaning diet; vegetable or fruit purees can be combined with added oil or cream (and a prescribable protein supplement if necessary) to maintain the correct ketogenic ratio. The progression onto meat and fish will allow for more variety. Finger foods tend to be higher in carbohydrate, however appropriate KD choices could include boiled carrot sticks, cubes of cheese, avocado, or soft pieces of fruit such as banana, soft pear or slightly cooked apple. Weaning breakfasts on the KD could include slices of omelette or hard-boiled egg, pieces of slightly mashed or soft fruit, with a ketogenic ‘yoghurt’ made with Ketocal and crème fraiche (Dos Santos, 2012).

Free foods are very limited on the classical KD, and most are unsuitable for infants.

Supplementation
Requirements for vitamin, mineral and trace elements should be assessed on an individual basis, depending on the provision from the prescribed KD and age-specific nutritional requirements. Supplementation may be needed if an infant has low calorie

requirements or is not fully ketogenic formula-fed. On-going intake of all micronutrients should be closely monitored, and it is the responsibility of the individual dietitian to recommend the most appropriate supplement available for each child to ensure nutritional adequacy.

In some cases additional carnitine may be needed if blood levels of free carnitine fall. Alkalisation of the urine may also be required if there is increased risk or evidence of renal stones.

Initiation
Infants under 12 months will be admitted to their local hospital for initiation; medically stable children over 12 months old can start the diet at home with close supervision from their local team after a teaching program, including instructions on the daily home monitoring of blood or urine ketones and the management of possible early side effects such as excess ketosis and hypoglycaemia. The classical KD will usually be built up slowly to an initial 2:1 ratio; this initiation process will depend on the individual and the local centre protocol. Ketogenic ratio can be increased to 3:1 (or 4:1) if needed, depending on ketone levels, seizure control and dietary tolerance.

Fine tuning
Fine tuning and on-going modification of a KD are an essential part of the dietetic care and may involve alterations to the energy prescription or an increase or decrease of ketogenic ratio. These changes should be done in a stepwise process, making only one change at a time, to allow assessment of benefit. Other modifications may be the increase of protein intake with body weight and age changes, alterations in meal, snack or feed distribution to fit with lifestyle, and adjustments to micronutrient supplementation dose if other diet components are changed, or in line with age increase or blood test results. Medium chain triglyceride (MCT) supplement can be added in small amounts to an infant's diet if needed to improve ketosis and seizure control AFTER the initial 8 week period on diet treatment. However, if the dietitian feels that MCT supplementation is necessary within the 8 week trial period, this takes priority. If the diet remains a ‘classical’ KD (this is to be discussed on a case-by-case basis by dietitians and the Dietetic Assistant) then the participant should not have to be withdrawn from the trial, although it will still result in a protocol deviation.

Illness and medications
When an infant is ill the KD takes second place to the necessary treatment and medical assistance should always be sought if there is any concern about health. It is common for ketone levels to fluctuate during illness and seizures can also worsen. Local centres should all have illness protocols in place that are clearly explained to the families/caregivers.

All medications such as antibiotics or painkillers should be as low in carbohydrate as possible. Intravenous (IV) dextrose infusions should be avoided if possible but if continued IV support is necessary a small amount of dextrose may be needed to maintain blood glucose levels which can be monitored.

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Appendix 2 (AED consensus flowchart)