Statistical analysis plan

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Introduction

This analysis plan sets out the methods of analysing the predetermined primary and secondary outcomes of KIWE, which will be reported in the National Institute for Health Research, Efficacy and Mechanism Evaluation report at the end of the trial and also in the main peer review paper to result from this randomised controlled trial. It also sets out the interim analyses for the Data Monitoring Committee and the stopping criteria to be applied.

The analysis of this trial will conform to the CONSORT statement[1-3] and the appropriate standard operating procedures written by the Priment Clinical Trials Unit.

Further information on this trial can be found in the protocol version 10.0 (31/03/2021). The protocol is stored on: S:\FPHS_Priment_CTU\Projects\Current\CTIMPS\KIWE\6. Protocol\ KIWE Protocol V10.0 - 31 March 2021

Trial summary

Aim

To determine the effectiveness on seizure control of the ketogenic diet (KD) compared to alternative further antiepileptic drug (AED) treatment in children with epilepsy aged one month to two years who have failed to respond to two or more pharmacological treatments.

Objectives

To discover whether the KD reduces seizure frequency compared with a further AED.

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

Study population

Inclusion criteria

- Age between one month and 24 months of age (not beyond second birthday at baseline)
- Diagnosis of epilepsy confirmed
- At least an average of 4 seizures per week in the baseline period
- Failed response to previous trial of two AEDs. In the case of infantile spasms this could include a trial of corticosteroids.
- Children with written informed consent from parent/carer

Exclusion criteria

- Age less than one month or more than 24 months of age at baseline
- No secure diagnosis of epilepsy
- Less than 4 seizures/ week on average in baseline period
- Trial of less than two AEDs
- Continues on corticosteroids in two weeks prior to randomisation
- Metabolic disease contraindicating use of the ketogenic diet eg pyruvate carboxylase deficiency, MCAD from previous medical investigation and screening at baseline.
- Progressive neurological disease
- Severe gastroesophageal reflux
- Previous treatment with the ketogenic diet
- Concurrent participation in another clinical trial of an investigational medicinal product.
- Patients who are prescribed AEDs not listed in the trial IMPs
- Patients who have a listed contraindication as per the SmPC to any of the AEDs listed in the trial IMPs

Trial design

A non-commercial, open label randomised controlled multicentre clinical trial of children aged one months to two years of age with epilepsy who have failed to respond to two or more pharmacological treatments (AED or corticosteroids), comparing ketogenic diet to further AED. The study will be conducted in two phases: first we will carry out a pilot phase in two centres (Great Ormond Street Hospital for Children and Evelina Children's Hospital (now closed due to poor recruitment)). We have added further centres (Cambridge, Birmingham, Bristol, Leeds, Liverpool, Manchester, St George's, Newcastle, Nottingham, Oxford Leicester, Preston,

Sheffield, Aberdeen, Dundee, Edinburgh and Glasgow) over time and Patient Identification Centre (PIC) at Southampton.

The pilot trial recruitment ran from 01/2015 to 01/2016 and the full trial will follow that recruiting until 31/07/2021. Follow up will end on 30/09/2021.

Randomised treatments

Intervention:

The experimental intervention will be an eight-week trial of KD therapy. A KD Intervention Manual will be created and provided to sites to aid the dietary calculations (see Appendix 1 in the protocol).

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, that is, 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 participant's medical notes and case report form. Breast feeding can be continued on a KD, in combination with a ketogenic feed which will 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 performed as part of standard care and written in the seizure diaries), seizure control and daily home measure of urine ketones. The latter can be used to ascertain adherence with the dietary restrictions.

Control

The control treatment 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, and chosen by the expert clinician responsible for management of the participant's epilepsy (see Appendix 2 of the protocol). Paediatric neurologists will meet at an 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 and healthy eating will be undertaken with participants' families of on Day 8 or 15 (+/- 2 days) at the randomisation visit after baseline.

Sample size

For the primary outcome, based on data from Neal et al[4], 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 ICC 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.

Randomisation

The randomisation schedule will be independently generated and held by Sealed Envelope[5]. 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.

There will not be any blocking or stratification.

Blinding

Parents, paediatric neurologists and dietitians will not be blind to allocation. The statistician performing the final analysis (LM) will not be actively informed which group is the intervention and control. However, as there will be unequal group sizes recruited, it will be possible to work them out.

LM will attend the Data Safety and Monitoring Board meetings and if necessary become unblinded to randomised allocation. NF will attend the Trial Management meetings and will remain blind to allocation until after final data analysis.

Outcomes

Primary Outcome

The total number of seizures experienced during weeks 6 to 8 of the intervention/ additional AED. This will be documented by the parents in their child's seizure diary.

Secondary outcomes

8 weeks

Whether seizure free using the parent reported seizure diary in weeks 6 to 8 of the intervention/ additional AED. This will be dichotomous – seizure free versus not seizure free.

Responder rate This is defined as the number showing more than a 50% 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). This will be dichotomous; responded to treatment versus did not respond to treatment using the definition above.

Tolerance to KD as assessed by questionnaire and blood results for C10 fatty acids in the blood.

12 months

12-month data will not be available for all participants recruited because of financial constraints related to the end of the study. 12-month analysis will take place with data accumulated by the time the database is locked when all the 8-week data have been collected.

Retention on treatment defined as number still on the ketogenic diet at 12 months (intervention group only)

Quality of life measured by the Infant Toddler Quality of Life Questionnaire (KINDL)[6, 7]. There are 97 items that comprise nine multi item concepts, two global concepts and two single items. For each concept, items are scored and summed then scaled so that they produce scores between 0 and 100. These are not designed to be summed to one scale, so each one will be used as an outcome. Scores are calculated if at least half of the items within a concept have been completed.

Neurodevelopment will be measured by the Vineland Adaptive Behaviour Scales, second edition[8]. It is assessed by parental rating of behaviours in communication, daily living skills, socialization and motor skills. Items within a domain are scored to give domain scores. The domain scores can then be combined to derive an overall score. Both the domain scores and the overall score will form the outcome.

Data collection

Data will be collected at screening, baseline, randomisation, 4 weeks, 8 weeks, 6 months, 9 months and 12 months. However, not all participants will have been followed up beyond 8 weeks.

Screening
Inclusion/ exclusion criteria
Review of medical history
Complete physical examination (includes weight, length, head circumference, general examination)

Baseline
Concomitant Medications (if appropriate)
Haematology
Biochemistry
Urinalysis
Other symptom directed examinations and results (if appropriate)
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)
KINDL
Seizures (diary)
Vineland Adaptive Behaviour Scales

Food diary

Randomisation
Eligibility criteria
Concomitant Medications (if appropriate)
AED medications (if appropriate)
Trial intervention (ketogenic diet or further AED)
Other symptom directed examinations
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)
Seizures
Ketones
Special assay (ketogenic diet group only)

4 weeks
Concomitant Medications (if appropriate)
Trial intervention (ketogenic diet)
AED medications (if appropriate)
Other symptom directed examinations and results (if appropriate)
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)
Seizures
Ketones
Side effects

8 weeks
Blood and urine test results (ketogenic diet group only)
Concomitant Medications (if appropriate)
AED medications (if appropriate)
Other symptom directed examinations and results (if appropriate)
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)
Seizures
Ketones
Special assay (ketogenic diet group only)
Side effects
KINDL

6 months
Concomitant Medications (if appropriate)
Other symptom directed examinations and results (if appropriate)
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)

Haematology
Biochemistry
Urinalysis
Seizures
Side effects

9 months
Concomitant Medications (if appropriate)
Other symptom directed examinations and results (if appropriate)
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)
Seizures
Side effects

12 months
Anthropometrics
Concomitant Medications (if appropriate)
Other symptom directed examinations and results (if appropriate)
Blood pressure (if appropriate)
Pulse (if appropriate)
Temperature (if appropriate)
ECG results (if appropriate)
Haematology
Biochemistry
Urinalysis
KINDL
Seizures
Vineland Adaptive Behaviour Scales
Side effects

Ongoing
Adverse events

Data entry

Data will be entered using a web based system set up by Sealed Envelope[5]. This has been set up so that, it mirrors the data collection sheets in order. It also has range checks, consistency checks and for closed questions gives a number of options plus "other" where appropriate. Data filled in on paper CRF (which will include food diaries) will be entered by the local sites. Seizure diaries will be entered by personnel at the trial management office. Assessors who will be entering the data will have no access to the group allocation through this system.

Data will be checked by the Statistician before analysis and any problems reported to the Trial Manager, who will rectify them as appropriate before data analysis.

Statistical analyses

To maintain the blinding of the statisticians (notwithstanding the blinding section above), one statistician will perform the interim analyses (LM) for the Data Safety and Monitoring Board and the other statistician (NF) will attend Trial Management Group meetings. LM will perform the final analyses and NF will check the primary outcome of the final analysis.

Interim analyses

Overall baseline demographic characteristics will be presented.

Serious adverse events (safety), will be dichotomised to the participant has experienced at least one serious adverse event versus has not experienced a serious adverse event. This will be analysed using a one sided Fisher's exact test.

Alpha spending and stopping criteria

There are no interim analyses conducted as part of the main trial analyses. The following are included for information, and are the planned analysis plan for the DSMB conducted independently of the trial management for the purpose of ensuring safety of participants included in the trial.

Using an overall p-value to indicate statistical significance of <0.05, and assuming there are three DSMB meetings which require interim analyses (when 25%, 50% and 75% of primary outcome data have been collected) in addition to the final analysis at the end of the study, then using the program ld98 (DOS version)[9], two stopping rules are to be established for the DSMB. The first, for efficacy (the primary outcome) uses the O'Brien Fleming[10] type rule while for safety (adverse events) a power family with an exponent of 1.5 is used. These give different p-values at each time point, set out in Table 1. These analyses are intended but may or may not have been conducted by the DSMB (and are included here only for information).

Table 1: Timing of interim analyses and p-values to be used to indicate efficacy and safety.

Time	Efficacy p-value	Safety p-value
0.25	0.00001	0.00313
0.50	0.00152	0.00571
0.75	0.00812	0.00740
1.00 (end of the trial)	0.01535	0.00876

Final analyses

All analyses will be intention to treat. The final analysis will use two sided p<0.05 to indicate statistical significance for the primary outcome.

Descriptive statistics

Initial analyses will look at summary statistics for all variables, both overall and by randomised group. Summary statistics for continuous variables will be mean, median, SD, lower quartile, upper quartile and reported appropriately according to distribution.

Analysis of the primary outcome

The primary outcome will be total seizure count in the weeks 6 to 8 of the intervention period accounting for 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 the $\log_e$ (baseline seizures/ number of measurement days). Observations will be linked using random intercept terms. Centres in the KD group will be included as random effects. Log_e number of days the outcome represents will be included as the offset. Degrees of freedom for the treatment effect will be derived from the number of participants in the analysis. Difficulties with model convergence which cannot be addressed by using different model optimisation procedures will be addressed by dropping the random effects for clustering of therapists within sites.

Analysis of the secondary outcomes

Dichotomous outcomes 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 using analogous strategies to that employed for the primary analysis, but with appropriate error terms and link functions.

Missing data

It is inevitable that there will be some missing data, however, every effort will be made to minimise this.

Analysis will be carried out to assess the potential impact of missing data on the primary outcome. This will be done by assuming those who have missing data in the intervention group have the maximum total number of seizures for that randomised group and time point, and the treatment as usual group will be assigned the median total number of seizures (worst case scenario).

Multiple imputation will not be carried out.

The primary analyses will be complete case and analyses looking at the impact of missing data will be considered supportive.

Supportive analyses

Adjusting for medium chain fatty acids

Therapist effects may be investigated further in supportive analyses[11].

References

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