Imperial College London

A Randomised Controlled Trial Assessing the Impact of a Low Calorie Diet on Weight Loss in Obese Patients with Type 2 Diabetes Mellitus Treated with Insulin

Trial registration number: ISCRCTN 21335883

Statistical Analysis Plan

Version Number	Effective Date	Protocol Version Number
1.0	*20/March/2018*	*1.0*

This Statistical Analysis Plan has been approved by:					
Author:	*Mr Omar Omar*	Signature:		Date:	

Reviewer:		Signature:		Date:	
Chief Investigator:		Signature:		Date:	
Name of Blind Reviewer (if required; otherwise insert N/A):	*NA*	Signature:	NA	Date:	NA

Version number	Effective date	Protocol version number	Details of changes (refer to section number of SAP)	Reason for change	Timing of change with respect to interim/final analysis
0.1	25/01/2018	1.1	First release (summary analysis plan)	-	-
1.0	20/03/2018	1.1	Expanded on the analysis plan and included further details on most of the sections	A detailed analysis plan to replace the summary analysis plan	Prior to final analysis commencing

Abbreviations & Definitions	
Abbreviation / Acronym	**Meaning**
DMC	Data Monitoring Committee
CONSORT	Consolidated Standards of Reporting Trials
ISCRCTN	International Standard Randomised Controlled Trial Number
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T2D	Type 2 Diabetes Mellitus
LED	Low Energy Diet
GSC	Gold Standard Control
SD	Standard Deviation
95% CI	95 Confidence Interval
AUC	Area Under the Curve
Term	**Definition**
International Standard Randomised Controlled Trial Number	A clinical trial registry
Protocol	Document that details the rationale, objectives, design, methodology and statistical considerations of the study
Randomisation	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Statistical Analysis Plan	Pre-specified statistical methodology documented for the trial, either in the protocol or in a separate document.

Contents

1. Introduction

This document gives a detailed statistical analysis plan for the trial and should be read in conjunction with the current trial protocol. Any deviations from this plan will be described in the final report or publication (see Table 1 final report template).

2. Background and rationale

The background and rationale for the trial are outlined in detail in the protocol. In brief this study test the hypothesis that weight loss through a low calorie diet can result in significant weight loss and improvement in diabetes in obese T2D patients.

3. Study objectives

The principal objective is to assess the impact of a low calorie diet on weight loss in insulin-treated patients with T2D and obesity.

Secondary objectives are as follows:

- To assess the effects of low calorie diet on: body composition, diabetes control, insulin use, glucose variability, effects on appetite and hunger, beta-cell function, other diabetes medications, cardiovascular risk factors (including obstructive sleep apnoea), and quality of life.

4. Study design

This is a prospective, unblinded, parallel group, randomised controlled trial. Patient participants will be identified via local GP practices, other healthcare professional and from the Diabetes Research Network. Participants will be randomised in a 1:1 ratio to Cambridge Weight Plan Group or routine care group.

5. Study comparisons

All references in this document to 'group' refer to prophylactic Cambridge Weight Plan Group or routine care group. The Cambridge Weight Plan is a diet programme commercially available in the UK and commonly used by individuals for weight loss. It is a stepped programme that includes both very low and low calorie intake stages. This study will use 800 calories as a benchmark

6. Outcome measures

6.1. Primary outcome(s)

The primary outcome in this study is weight loss at 12 months.

6.2. Secondary outcomes

The secondary outcomes are as follows

- body composition
- diabetes control
- insulin use
- glucose variability
- other diabetes medications
- beta-cell function
- to determine effect on hunger and appetite
- cardiovascular risk factors

- quality of life.

7. Randomisation

Participants will be randomised on-line via a secure internet facility through an online software tool (Sealed Envelope Ltd). Subjects will be randomised to either to the formula low energy diet programme (LED; intervention) or gold standard clinical care (GSC; control) in a 1:1 ratio. To ensure balance of potential confounders (age, gender, ethnicity, diabetes duration) between intervention arms, minimisation method was used, allowing optimal balance in the stratifying factors. In addition a 30% chance of simple random allocation was included. Due to nature of the intervention the subjects could not be blinded.

8. Sample size

To achieve a clinically significant 10 kg weight loss between groups (SD 15 kg) at a 5% significance level with 80% power, a sample size of 74 participants was required. From the literature the mean attrition rates while following a very low energy diet and low energy diet are between 0 to 52%. Accounting for approximately 20% drop out a total of 90 participants were recruitment (45 per arm).

9. General statistical considerations

9.1. Analysis populations

All primary analyses (primary and secondary outcomes) will be by the intention to treat principle. Patients will be analysed in the treatment group to which they were randomised, and all patients shall be included whether or not they received the allocated treatment. This is to avoid any potential bias in the analysis.

9.2. Handling of protocol deviations and violations

We will apply a strict definition of the intention-to-treat-principle and will consider all randomised patients in the analysis in some form regardless of deviation from the protocol[1]. This includes patients who were randomised but later found to violate the inclusion or exclusion criteria. It does not include those participants who have specifically requested to withdraw the use of their follow-up data in the first instance; however these outcomes will be explored as per other missing responses

9.3. Levels of confidence and p-values

Unless otherwise specified, estimates of differences between groups will be presented with 95%, two-sided confidence intervals. P-values will be reported from two-sided tests at the 5% significance level.

9.4. Adjustments for multiplicity

No correction for multiple testing will be made.

9.5. Interim analysis and stopping rules

Not applicable; No planned DMC or interim analysis

9.6. Timing of primary analysis

The primary analysis for the study will occur after the last randomised participant entered into the trial has completed 12 months follow-up.

9.7. Timing of other analyses

Not applicable; no longer-term analysis following the primary analysis is proposed.

9.8. Covariate adjustment

In the first instance, comparative estimates of differences between groups will be adjusted for the parameters listed in section 7 for the primary outcome only. Age at randomisation and duration of diabetes will be treated as a continuous variables in this adjustment. If covariate adjustment is not practical, unadjusted estimates will be produced and it will be made clear in the output why this occurred (e.g. not possible due lack of model convergence).

9.9. Handling missing data

In the first instance, analysis will be completed on received data only with every effort made to follow-up participants even after protocol violation to minimise any potential bias. To examine the possible impact of missing data on the results, and to make sure we are complying with the intention-to-treat principle, sensitivity analysis will be performed on the primary outcome measure.[2] See section 10.6 for further details.

9.10. Distributional assumptions and outlying responses

Distributional assumptions (e.g. normality of regression residuals for continuous outcomes) will be assessed visually prior to analysis; although in the first instance the proposed primary method of estimation in this analysis plan will be followed. If responses are considered to be particularly skewed the impact of this will be examined through sensitivity analysis; this will consist of transformation of responses prior to analysis (e.g. log transformation) in the first instance. If extreme values are apparent and considered to be affecting the integrity of the analysis, sensitivity analysis consisting of removing the outlying response(s) and repeating the base analysis will be performed. Output from these analyses, if performed, will be described and presented alongside the base case analysis (or included, e.g. in appendices) with the excluded values clearly labelled.

9.11. Data manipulations

The Trial Statistician will derive all responses from the raw data recorded in the database. Where data of birth is provided, age will be calculated as time from date of birth to date of randomisation.

10. Proposed statistical methods

10.1. Study population

A flow diagram (recommended by CONSORT[3]) will be produced to describe the patient flow through each stage of the study.

Numbers and description of reasons (where available) will be provided at each stage, e.g. reasons withdrawing from study or why participants did not receive the allocated treatment. The following items (number of participants) will be described:

- Assessed for eligibility
- Eligible
- Randomised (by group)
- Received allocated treatment/did not receive allocated treatment (by group)
- Withdrawn/lost to follow-up (by group)
- Included in the primary analysis (by group)

10.2. Baseline characteristics

Categorical data will be summarised by number of responses, frequencies and percentages. Continuous data will be summarised by the number of responses, mean and standard deviation if

deemed to be normally distributed and number of responses, median and interquartile range if data appear skewed. Tests of statistical significance will not be undertaken.[4]

10.3. Analysis methods – primary outcome

The primary endpoint of weight loss at 12 months will be analysed repeated measures analysis of covariance using a mixed model to take account of the within-subject variability, using weight measurements at all post-randomisation time points and adjusting for baseline weight, randomisation factors (age, gender, ethnicity and diabetes duration), HbA1c and number of medications. The adjusted mean group differences for baseline and each time point with 95% CIs will be calculated but the primary time of interest is at 12 months. Both the crude unadjusted and adjusted estimates will be presented, but the primary inference will be based on the adjusted analysis.

10.4. Analysis methods – secondary outcomes

Secondary outcomes will be analysed using similar methods as above. Difference in the frequency of hypoglycaemic episodes between the groups was compared using mixed-effects Poisson regression with incidence rate ratio presented. Area under the curve (AUC) will be calculated using the trapezoidal rule.

10.5. Analysis methods – exploratory and other outcomes

Not Applicable

10.6. Sensitivity analyses

To examine the possible impact of missing outcomes on the overall results, sensitivity analysis will be performed. This will be limited to the primary outcome measure (weight loss at 12 months) and will consist of:

- Subset of those who completed the 12 month follow-up;
- Multiple imputation by chained equation[5]. Twenty imputed datasets will be created by replacing missing values with simulated values from a set of imputation models built from all potential prognostic and the outcome variable (weight loss). Analysis will be then be performed on each set with the results combined using Rubin's rule[6] to obtain a single set of results (treatment effect estimate and confidence intervals);
- Last observation carried forward. i.e imputing a missing value with the last known value

10.7. Planned subgroup analyses

Interpretation of subgroup analysis will be treated with caution[7]. Analysis will be restricted to the following subgroup:

- Those in the LED group who will cease insulin usage compared to those who don't cease insulin usage

10.8. Safety data

The number and percentage of patients experiencing any serious adverse event (SAE) will be presented by group. Statistical significance will be determined by chi-squared test. The total number of SAEs in each group will also be given along.

11. Output from sub-randomisations

Not Applicable

12. Health economic analyses

Not Applicable

13. Statistical software

Stata Special Edition Version 15.0 (StataCorp LP, College Station, TX) and SPSS v.25.0 (IBM Corp., Armonk, NY, USA) will be used for all analyses.

14. References

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3. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340:c332.
4. Altman DG, Dore CJ. Randomisation and baseline comparisons in clinical trials. Lancet. 1990; 335:149–153.
5. Royston P. Multiple imputation of missing values: update of ice The Stata Journal 2005;5:527-36.
6. Rubin D. Multiple imputation for nonresponse in surveys. New York: Wiley, 1987
7. Wand R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Reporting of subgroups analyses in clinical trials. NEJM. 2007; 357:2189-2194.