STATISTICAL ANALYSIS PLAN

Study Title:
Dietary approaches to the management of type 2 diabetes (DIAMOND)

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INTRODUCTION

PREFACE

The Investigators (Dr Elizabeth Morris, Prof Susan Jebb, Prof Paul Aveyard), and Assistant Trial Manager (Dr Michaela Noreik) have contributed to and approved the statistical analysis plan (SAP). The SAP supports the study protocol version 2.0 and dated 1/3/2018. Analysis will be carried out using up-to-date versions of Stata.

PURPOSE AND SCOPE OF THE PLAN

The purpose of the plan is to complete the main analysis as stated in the protocol.

TRIAL OVERVIEW

This study aims to investigate the feasibility of delivering a low-carbohydrate, low-energy, food-based dietary intervention in primary care, to patients with type 2 diabetes who are overweight. The intervention draws upon the motivational importance of the relationship between the GP and the patient, but provides almost all technical knowledge through the use of structured materials such as meal plans, thus addressing the uncertainty that health professionals have about nutrition. Likewise, we aim to improve patients' adherence to the programme by providing a structured simple behavioural support programme for staff to use when implementing this programme.

The hypothesis is that compared to usual care, an intervention involving targeted health professional advice and goal setting, will help patients understand and adhere to a low-carbohydrate, low-energy diet that will lead to significant reductions in weight and improvements in glycaemic control, providing positive reinforcement of the dietary modification. In the longer term, the energy content of the diet can be increased, but adherence to a lower-carbohydrate diet offers the potential for sustained glycaemic control. Together with a return to a low-energy regimen in the case of weight regain, this dietary strategy provides the foundations for a sustainable long-term approach to the management of this chronic condition.

Specific aims of this research are:

i. To investigate the feasibility of delivering this behavioural and dietary intervention to a population of patients with diabetes in primary care, and determine whether progression to the development of a full scale randomised controlled trial is indicated.
ii. To assess achievements against a number of process measures to inform future trial design.
iii. To investigate the potential physical, biochemical, and economic impact of this behavioural and dietary intervention.

OBJECTIVES

Primary objective

The primary objective of this study is to test the feasibility of a low-carbohydrate, low-energy, behavioural intervention, comprising targeted advice from a health professional combined with written dietary information, to promote weight loss and improved glycaemic control in patients with type 2 diabetes. This feasibility study will then determine whether to progress to a full randomised control trial.

The measures of feasibility are:

1. The proportion of allocated intervention group participants who attempt the dietary intervention after randomisation.
2. Fidelity of intervention delivery: The proportion of essential elements included in intervention delivery session.
3. The proportion of participants that attend the final follow-up session

Secondary objectives

To assess the study processes:

1. Percentage of eligible patients, as a proportion of the total population of patients in a practice, with type 2 diabetes.
2. Percentage of people who fulfil the recruitment criteria who accept the invitation to participate
3. Proportion of patients who enrol in the study who are deemed to have with 'suboptimal control' (HbA1c above the National Institute for Health and Care Excellence target of ≥7%).
4. Participant adherence to the protocol, including:
    - Change in dietary composition (low-carbohydrate, energy restricted—assessed using 24 hours dietary recall questionnaires)
    - Participants' self-reported concordance with the intervention
    - Availability of data for outcome measures
    - Attendance at follow-up sessions
    - Contamination of the control group (ie, those who choose to follow the principles of the intervention (ie, follow a low-carbohydrate diet), despite being allocated to the control group). This will be assessed using 24 hours dietary recall questionnaires to establish change in dietary composition (frequency of carbohydrate consumption, energy restriction) of control group participants.
5. Difference between 'baseline' HbA1c value and that used from the latest record as inclusion criteria.
6. Serious adverse events (SAEs) reported up to the end of the 12-week study participation period.

To test the effects of the intervention on:

1. Change in HbA1c—number of patients previously in diabetic HbA1c range, now in 'at risk of diabetes' (6%–6.4%) or 'diabetes in remission' (<6.0%, off medications) HbA1c range.
2. Change in fasting glucose, fasting insulin, Homeostasis Model Assessment steady state beta cell function (HOMA-%B) and insulin sensitivity (HOMA-%S).
3. Change in weight.
4. Change in diabetic medication (number of diabetic medications currently prescribed to the patient; dose of diabetic medications; initiation of new medication during study period; initiation of insulin; initiation of injectable diabetic medication; number of medications stopped or changed during the study period).
5. Change in lipid profile—total cholesterol, high-density lipoprotein (HDL), triglycerides, calculated non-HDL cholesterol and total cholesterol:HDL ratio.
6. Change in liver function tests (bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, AST:ALT).
7. Change in BP (systolic, diastolic).
8. Change in antihypertensive medication (number of medications started and stopped during study period; dose of antihypertensive medications; initiation of new medication during study period).
9. Change in medication prescribing costs (total and diabetic) across study group and total practice diabetic population.
10. Effect on patient's Problem Areas in Diabetes (PAID) score.

Qualitative outcomes:

1. Acceptability and experience of intervention, for patients and healthcare professionals

TRIAL DESIGN

This feasibility study is an individually randomised controlled trial, performed in adult patients with type 2 diabetes and a BMI ≥30kg/m2. Each participant will be randomly allocated on a 2:1 basis to the active intervention (DIAMOND programme, detailed in section 8.1 of the study protocol) or control (usual care).

Each participant will be enrolled for 3 months from randomisation to final follow up, and will attend up to a total of up to 7 visits. Data collection will be in the form of participant self-reporting questionnaires, healthcare professional feedback, and biometric and biochemical measurements (weight, waist circumference, HbA1c, fasting glucose, etc).

Due to the nature of the intervention, it will not be possible to blind the participants, clinicians delivering the intervention, or some of the study team to the treatment allocation once the study commences, but they will be blind at the point of randomisation.

OUTCOMES MEASURES

PRIMARY OUTCOME

Primary Objective	Measures	Timepoints
To test the feasibility of a behavioural and dietary intervention, delivered in primary care, aiming to promote weight loss and improved glycaemic control, and determine whether to progress to full scale RCT	1. The proportion of allocated intervention group participants who attempt the dietary intervention after randomisation. 2. Fidelity of intervention delivery: The proportion of essential elements included in intervention delivery session. 3. The proportion of participants that attend the final follow-up session	1. Nurse documentation at intervention visit 2. Evaluation of transcribed consultations against checklist of essential elements 3. Number of participants attending final study visit

SECONDARY OUTCOMES

Objectives	Outcome Measures	Timepoints of evaluation of this outcome measure
Secondary Outcomes:		
Effectiveness measures		
1. Glycaemic control **2. Body weight**	1. Change in HbA1C (including change in number of patients classified as having an HbA1c in the "diabetic", "at risk of diabetes", or "diabetes in remission" range). 2. Change in fasting glucose, fasting insulin, converted into HOMA-B and HOMA-S 3. Change in diabetic medication (number and dose of diabetic medications; initiation of new medication during study period; initiation of insulin; initiation of injectable diabetic medication) 4. Change in weight 5. Change in BP (systolic, diastolic) 6. Change in antihypertensive medication 7. Change in lipid Profile 8. Change in LFTs (AST:ALT) 9. Change in medication prescribing costs (total and diabetic)	1-10. Mean value at baseline and 3 months

3. Blood pressure **4. Other markers**	across study group and total practice diabetic population 10. Effect on patient's problem areas in diabetes (PAID) score	
Process Measures	1. Percentage of eligible patients, as a proportion of the total population of patients in a practice, with type 2 diabetes. 2. Percentage of people who fulfil the recruitment criteria who accept the invitation to participate 3. Proportion of patients who enrol in the study who are deemed to have with 'suboptimal control' (HbA1c above the National Institute for Health and Care Excellence target of ≥7%). 4. Participant adherence to the protocol, including: o Change in dietary composition (low-carbohydrate, energy restricted—assessed using 24 hours dietary recall questionnaires) o Participants' self-reported concordance with the intervention (follow up visit CRFs) o Availability of data for outcome measures o Attendance at follow-up sessions o Contamination of the control group (ie, those who choose to follow the principles of the intervention (ie, follow a low-carbohydrate diet), despite being allocated to the control group). This will be assessed using 24 hours dietary recall questionnaires to establish change in dietary composition (frequency of carbohydrate consumption, energy restriction) of control group participants. 5. Difference between 'baseline' HbA1c value and that used from the latest record as inclusion criteria. 6. Serious adverse events (SAEs) reported up to the end of the 12-week study participation period.	
Qualitative Sub-study **Acceptability and experience of intervention, for patients and healthcare professionals**	Qualitative focus groups with participants and practitioners. Themes and sub-themes pertaining to the participants' (i) knowledge (ii) perceived barriers, facilitators and actions, (iii) contextual influences, as well as experience of the programme training and materials.	After completion of the study programme.

TARGET POPULATION

Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18 years or above.
- BMI of ≥30kg/m2
- Diagnosed with type 2 diabetes, as defined by an HbA1c ≥48mmol/mol at diagnosis.
- Patients must have undergone diabetic retinopathy screening within the last 12 months.

Exclusion Criteria

- History of, or features suspicious of, an eating disorder
- Pregnant, breastfeeding, currently undergoing fertility treatment, or planning to become pregnant during the course of the study
- Recent MI or CVA (<3 months)
- Uncontrolled ischaemic heart disease, critical ischaemia, uncontrolled hypertension, uncontrolled cardiac arrhythmia (eg inadequate rate control in AF, inadequate episode control paroxysmal AF), cardiac conduction abnormality (eg long QT syndrome)
- Cardiac failure (Grade II New York Heart Association, and more severe)
- Renal failure (CKD Stage 4 or 5)
- Active treatment for cancer (other than skin cancer treated with curative intent by local treatment only)
- Intercurrent serious infection at time of recruitment
- Diagnosed with a significant psychiatric disorder or substance abuse
- Serious neurological disorder, including epilepsy
- Recently undergone significant surgery (<6months)
- History of bariatric surgery, including gastric banding
- Are currently using a “fasting”/low-energy diet
- Unwilling to consider any dietary changes
- Unable to understand English
- Are currently using insulin therapy, or SGLT2 inhibitors (Glifozins – eg empaglifozin, dapaglifozin, canaglifozin).
- Non-proliferative retinopathy level R2 or worse (ie, any level more severe than “background” non-proliferative diabetic retinopathy, R1), proliferative diabetic retinopathy, or maculopathy.
- HbA1c ≥ 93mmol/mol (10.5%)
- Recruiting physician feels they are inappropriate for recruitment due to any other reason.

SAMPLE SIZE

The total number of participants we intend to recruit for this study is 30, with a sampling ratio of 2:1. Therefore, 20 participants will be allocated to the active intervention, and 12 participants will be allocated to the control group.

In determining thresholds for progression criteria, based on previous trials of a similar nature, we expect a drop-out rate of 25%, and expect that the first two criteria would achieve 75-80%(13, 46). Therefore based on a 95% confidence interval around this achievement, progression criteria have

been set at 60% for each of these outcomes (based on a sample size of 30 participants, allocated intervention:control group in a 2:1 ratio).

RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

An independent researcher (Melina Tsiountsioura) generated the randomisation sequence following the study randomisation plan (V1.0) and uploaded the randomisation sequence to the electronic TMF in an encrypted file.

Randomisation was performed using the platform www.randomization.com using permuted block design in blocks of 3 (then stratified by practice), in a 2:1 intervention:control ratio. Allocation was then concealed in sequentially numbered opaque envelopes by the independent researcher (MT).

To ensure the allocation concealment has not been broken, the intended randomisation sequence will be compared with the sequential allocation of treatment groups to participants, by comparing the randomisation card from each sequentially numbered envelope with the allocation of participants at randomisation.

Investigators were not blinded to intervention allocation but the primary outcomes are measures of participant consent to attempt the intervention (intervention arm only), and follow up (all participants), as well as fidelity of intervention delivery against a pre-specified checklist, developed by the co-investigators before the first participant attended their intervention visit. The fidelity assessment will be completed by two independent researchers (MN and EM) and any discrepancies discussed with a third reviewer (SJ/PA).

ANALYSIS – GENERAL CONSIDERATIONS

DATA CLEANING

Prior to the final data lock, data cleaning will be performed, including checking outcome variables are in the correct ranges.

DESCRIPTIVE STATISTICS AND PARTICIPANT CHARACTERISTICS

A table will present the baseline characteristics by trial arm and overall (Appendix 1). The table will include age, gender, ethnic group, BMI, HbA1c, blood pressure, education, duration of diabetes and relevant medications. Continuous variables will be summarised using means and standard deviations. Medians with interquartile ranges will be presented where appropriate. Categorical variables will be summarised using counts and percentages. Data will be analysed using Stata.

Baseline characteristics will be coded as: age (years); gender (men, women); ethnic group (White, Black, Asian, Mixed, Other); BMI (kg/m2); blood pressure (mmHg, average of readings 2 and 3); HbA1c (mmol/mol), education (none, secondary education, higher education); duration of diabetes (years), diabetes with suboptimal control at baseline (HbA1c above the National Institute for Health and Care Excellence target of ≥7%), and relevant medications (e.g. diabetic medications, antihypertensive medications).

Definition of population for analysis

The primary statistical analysis of outcomes will be carried out on the basis of intention-to-treat (ITT) (based on the trial arm to which participants were initially randomised) to analyse all participants who complete the study (available case analysis). We will endeavour to obtain full follow-up data on every participant to allow full ITT analysis, but we will inevitably experience the problem of missing data due to withdrawal, loss to follow up, or non-response to questionnaire items.

Data Monitoring Committee And Interim Analyses

Due to the low risk of harm and short length of the intervention, a data monitoring committee will not be needed and an interim analysis will not be conducted.

Primary analysis

Primary outcome

The primary outcome analysis will use the intervention visit CRF; the final attendance data for 12 week follow up sessions; and the audio-recordings of intervention visits.

The primary analysis will test for:

- The proportion of participants randomised to the intervention group willing to attempt the intervention;
- The proportion of participants who attend the final follow up session
- The proportion of intervention delivery sessions which contain at least 60% of essential elements present; and the proportion of essential elements contained in the intervention sessions.

We will calculate confidence intervals around the proportions using the OpenEpi platform (https://www.openepi.com/Menu/OE_Menu.htm).

Handling missing data

The percentage and absolute withdrawal and participants lost-to-follow up will be reported for each study arm in the CONSORT flow-chart and reasons for missing data will be documented.

For those who withdraw or who are lost to follow up, we will assess the sensitivity of the analysis to different assumptions about missing data using two imputation methods commonly used: completer only analysis and baseline observation carried forward.

Handling outliers

For the analysis of the primary outcomes, we do not expect significant outliers.

For the secondary outcomes, in particular biochemical tests (such as liver function, lipid profile), any “implausible” values will be checked with the sites and patient records. If information has been provided such as new, un-related diagnoses that may account for the outlier values, these will be excluded from the primary analyses.

We will conduct a sensitivity analyses in which control group participants who have self-identified as actively now following a low-carb diet, or coded as "contaminated" dietary advice with a significant change in carbohydrate content of their diet in repeat FFQ at 12 weeks, are removed analyses for weight and HbA1c change, to determine the impact of these participants.

SECONDARY ANALYSIS

EFFECTIVENESS MEASURES

Between the intervention and control groups, linear regression models (ANCOVA) will be used to test for:

1. From clinical measurements: a difference in the change (from baseline to follow up) in weight, BMI, HbA1c, fasting glucose, fasting insulin, HOMA-B and HOMA-S, lipid profile (total cholesterol, HDL, triglycerides, calculated non-HDL cholesterol, and total cholesterol:HDL ratio), liver function (bilirubin, ALT, AST, ALP, albumin, AST:ALT ratio), systolic and diastolic BP
2. For survey measurements: change in score (baseline to follow up)

The small sample size in this study precludes multiple adjustments for other variables, but we will report analysis adjusted for centre as this was a stratification variable. Additionally, in separate analyses, we will test the models with adjustment for any variables (one at a time) that show meaningful imbalance – for example, baseline values.

Change in medication measurements will be reported descriptively: number of diabetic and antihypertensive medications (baseline, follow up, and change); number of medications stopped and started over study period; number of medications reduced or increased in dose over study period. Median change in number and IQR, and mean number and standard deviation, will be calculated in both groups.

MODEL ASSUMPTIONS

The appropriateness of the normality, and homogeneity of variances assumptions required for the model will be assessed using residual and other diagnostic plots, the Shapiro-Wilk test of normality, and the Levene's test for equality of variances. Where concern is indicated, a transformation and/or a nonparametric method will be used to address gross deviations from the assumptions.

NON-EFFICACY OUTCOMES

<u>Process measures</u>

- Recruitment rates: we will report the number of participants who are invited, who accept the invitation, consent to take part in the study and are randomised at baseline.
- Representativeness of population: we will report the number of participants eligible for invitation to the study patients, as a proportion of the total population of patients in a practice with type 2 diabetes
- Participant adherence to the protocol, including: We will report change in dietary composition using 24hour dietary recall questionnaires at baseline, 8 and 12 weeks (baseline to 8 weeks, and baseline to 12 weeks); participants' self-reported concordance with the

intervention (number of participants self-reporting adherence to each of the three primary dietary goals); number of participants who attend each follow up session; Contamination of the control group – change in carbohydrate content of the diet of the control group using 24hour dietary recall questionnaires at baseline and 12 weeks, as well as self- or nurse-reported adherence to a low carb diet.

- Other process measures: difference between 'baseline' HbA1c value and that used from the latest GP record as inclusion criteria.
- We will report any serious adverse events (SAEs) reported up to the end of the 12-week study participation period.

Qualitative Sub-study

Verbatim transcriptions will be analysed using the NVivo 11 software programme. A thematic analysis approach will draw out themes and categories from the data. One researcher will deductively code the transcript data. A second researcher will check a sub-sample for validity and inter-rater reliability. In instances where it is unclear how to code themes, discussion with a third reviewer will reach consensus on whether to form a new theme or whether to expand an existing theme. Findings will be synthesised narratively.

SENSITIVITY ANALYSES

Sensitivity analyses will be conducted as follows:

- Using completer only analysis and baseline observation carried forward for those people with missing information at follow up.
- Excluding participants with a new, unrelated diagnosis during the course of the study which may lead to outliers in the data (e.g. new liver disease, new anaemia)
- Excluding control group participants identified as newly following a low-carbohydrate diet.

ADDITIONAL EXPLORATORY ANALYSIS

We will conduct exploratory subgroup analysis by gender, baseline HbA1c (<7% vs ≥7%), and duration of diabetes.

VALIDATION

The senior investigators will double check the analysis plan and will oversee the analysis process.

APPENDICES

Appendix 1. Template tables for presentation of results

Baseline characteristics of participants

N(%), unless otherwise specified	Control (n=)	Intervention (n=)	All (n=)
Age, years, mean (SD)			
Gender, female			
BMI, kg/m^2, mean (SD)			
HbA1c, mmol/mol, mean (SD)			
Blood pressure, mean (SD)			
Duration of diabetes, years, mean (SD)			
Suboptimal control of diabetes at baseline			
Ethnic group			
White			
Black / Asian			
Mixed / Other			
Education			
No formal qualifications			
Secondary education			
Higher education			
Relevant medications			
Number of diabetes medications			
Number of antihypertensive medications			