Imperial College London

PROTOCOL BOOKLET

Study Title: 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

Internal Reference No: 14HH2150_____

Ethics Ref: _12/WM/0199_____

ISRCTN: 21335883

Date and Version No: 0128/123/2016Version 1.109

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Sponsor:

Imperial College London is the main research Sponsor for this study.

For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at: AHSC Joint Research Compliance Office , Imperial College London, Room 221, Medical School Building, St Marys Campus, Norfolk Place, London, W2 1PG Tel: 0207 594 1872

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Synopsis

Study Title	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
Internal ref. no.	14HH2150
Trial Design	Randomised Controlled Trial
Trial Participants	Obese patients with Type 2 Diabetes who are currently on Insulin Therapy
Planned Sample Size	90
Planned Trial Period	~~36~~ 44months
Research Ethics	03 months
Planned Recruitment Period	32~~18~~ months
Intervention Period	06 months
Follow-up duration	06 months
Analysis	05~~3~~ months
Publications	03 months
Primary Objective	To assess the impact of a low energy diet based programme on weight loss in insulin-treated patients with type 2 diabetes and obesity
Secondary Objectives	To assess the effects of the programme 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

Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BMR	Basal Metabolic Rate
CWP	Cambridge Weight Plan
CI	Chief Investigator
CRF	Case Report Form
CVD	Cardiovascular Disease
ESS	Epworth Sleepiness Scale
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
Kcal	Kilocalories
LCD	Low Calorie Diet
OGTT	Oral Glucose Tolerance Test
MRP	Meal Replacement Products
PIL	Participant/ Patient Information Leaflet
PSQI	Pittsburgh Sleep Quality Index
PWF	Premature Withdrawal Form
RCT	Randomised Control(led) Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF	Site File
SOP	Standard Operating Procedure
T2D	Type 2 Diabetes Mellitus

Contents

1. Introduction

Type 2 Diabetes Mellitus

We are currently facing a major pandemic of obesity associated with increased prevalence of type 2 diabetes mellitus (T2D). T2D is associated with insulin resistance and insufficient insulin secretion to overcome this resistance. It was previously believed that the pathophysiology of diabetes involved a gradual reduction in insulin secretory capacity to eventually result in necessity for lifelong insulin treatment. This view has resulted in earlier introduction of insulin in patients. Also, the aim of managing diabetes complications has been to control blood glucose tightly. The combination of tight glucose control in combination with earlier introduction and intensification of insulin treatment has resulted in the exacerbation of obesity amongst patients with T2D. This has resulted in the vicious cycle of obesity and diabetes since greater obesity results in greater treatment requirements and vice versa (1). This vicious cycle has resulted in decreased quality of life, and increased mental stress, anxiety, and depression in T2D patients with obesity (2).

Over 350 million cases of T2D are predicted worldwide by 2030 (3). Over 2.8 million people in the UK are diagnosed with diabetes and it is anticipated that there are an additional 850 000 undiagnosed cases (4). T2D is the main cause of blindness, lower limb amputations, and renal failure (4, 5, 6). T2D is a progressive condition and its co-morbidities are interlinked with lifestyle and environmental factors such as excess consumption of nutritional poor diets and lack of physical activity (7, 8). The majority of T2D patients are obese (9) with increased central abdominal fat distribution which has been shown to act as an additional aggravating factor in the development of T2D and cardiovascular disease (10, 11). This has led to the intensified search for effective T2D treatments to reduce the mortality.

A large proportion of NHS budget is being spent on T2D treatment (12), which is costing the NHS nearly £10 billion per year (6). These strategies often encompass surgical, pharmacological, and dietary and/or lifestyle interventions (13). The introduction of novel therapies, such as the GLP-1 analogues, and bariatric surgery has now shown that loss of insulin secretion is not inevitable in T2D. The success of bariatric surgery in diabetes improvement and remission suggests that sufficient weight loss could have a major impact on diabetes in obese individuals (14). Furthermore, dietary and lifestyle interventions have been shown to be an important cornerstone of T2D management (11, 15). There is scope for more

effective, safe, and novel randomised controlled trials (RCTs) in T2D treatment that can establish whether a hybrid approach of long-term and sustainable low calorie diet (LCD) and lifestyle modification induced weight loss intervention can eliminate or at least reduce the need for insulin therapy. We therefore aim to 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.

1.2 Hypothesis

In obese type 2 diabetes patients treated with insulin, a 12 month dietary invention with LCD will result in greater weight reduction leading to significant improvement in glycaemic control compared to routine care.

In insulin treated T2D patients, the CWP, compared to the routine care group, expect to:

a. Greater percentage of patients achieving at least a 5% weight loss;
b. Improved body composition;
c. Improvement; in glycaemic control;
d. Reduction of the need of insulin therapy;
e. Improved beta-cell function
f. Better quality of life in T2D patients;
g. Improvement in cardiovascular risk factors.
h. Improved appetite and hunger control
i. Alterations in microbiome
j. Alterations in the metabolic profile
k. Improved glucose variability

1.3 Objectives

1.3.1 Primary Objective

To assess the impact of a low calorie diet on weight loss in insulin-treated patients with T2D and obesity.

1.3.2 Secondary Objectives

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.

2. Methodology

2.1 Design

This study is a prospective, parallel group, randomised controlled trial with a 1:1 ratio.

2.2 Participants

Adult obese patients, with T2D, who have been on insulin..

2.2.1 Eligibility Criteria;

Inclusion Criteria:

- Have BMI ≥30 kg/m²;
- Men or women;
- Age 18-70 years;
- Are willing and able to give informed consent for participation in the study;
- Insulin treatment less than 10 years or greater 10 years with a fasting c-peptide of ≥600

Exclusion Criteria:

- Have Type 1 diabetes;
- Any significant diabetes microvascular complication;
- Are unable to provide written informed consent;
- Have experienced a cardiovascular disease (CVD) event in the previous 6 months,
- Are at stage 4 chronic kidney disease or greater (eGFR <30 mL/min/1.73 m²);
- Have a mental incapacity, unwillingness and/or inability to understand and be able to complete the mental health questionnaires in the provided language;
- Currently pregnant, lactating, or planning pregnancy within the study period;
- Have a clinical diagnosis of binge eating disorder
- Patient has condition precipitating fluid overload such as heart failure (New York Heart Association grade III-IV) and liver cirrhosis;

• Are using medication clinically deemed to affect metabolic rate and weight
• Have significant psychiatric disorder (e.g. schizophrenia, anxiety, panic disorder,
• ADHD/ADD, post-traumatic stress disorder, obsessive-compulsive disorder);
• Uncontrolled depression;
• Have participated in a weight management drug trial in previous 3 months;
•Difficult to control International Normalising Ratio (INR) within the therapeutic range ;
• Have uncontrolled epilepsy;
• Are known or suspected of substance use;
• Are lactose intolerant;
• Severe musculoskeletal conditions preventing walking;
• Gout;
• Have active gallstone disease or known asymptomatic gallstones.
• Clinically assessed hypoglycaemia unawareness
• On ECG evidence of left bundle branch block

Withdrawal Criteria - the patient has the right to withdraw their consent anytime without giving any reason. Their decision to withdraw from the trial will not affect their future legal and medical rights (16). The patient's reason for withdrawal will be recorded on the premature withdrawal form (PWF). This will be shown to patients before obtaining informed consent. Patients will be notified that if they choose to withdraw from the study, the investigative team will not proceed with further assessments and data collection but their previously collected data will be used by the investigative team for research purposes. Patients will be given a withdrawal letter (appendix I) and a letter will also be sent to their general practitioner (GP) (appendix II). Also, the study will withdraw the patient if:

• The patient is unable to adhere to the study protocol and study requirements;
• There is a significant protocol deviation;
• The patient becomes pregnant during the study;
• Any new illness that affects their inclusion (exclusion criteria above);
• Continuing in this research is harmful to the patient health;
• The patient is lost to follow up;
• The trial cancels.

2.2.2 Study Site Locations

Potential participants will be identified from the Imperial College London, Imperial College London Healthcare NHS Trust, Central London Community Healthcare NHS Trust, primary care within North West London, the Hammersmith and Fulham Clinical Commissioning Group and the Clinical and Diabetes Research Network. Additional sites might be added in the future to achieve the recruitment target.

2.2.3 Recruitment

In primary care, eligible patient participants will be identified via local GP practices, other healthcare professional and from the Diabetes Research Network using the study inclusion/exclusion criteria, after which an invitation pack will either be sent by the general practice to eligible patients or given to them when they come for a clinic appointment. The invitation pack will contain an invitation letter (appendix III) and a patient information leaflet (PIL). The PIL will outline the details of the study. The invitation letter will have a reply slip (appendix IV), addressed to the research team, where patients can indicate their willingness to participate in the study or not. Patients who have not responded to the invitation letter will be sent a letter or telephoned approximately 2 weeks after initial contact. Alternatively, if a member of the research team is available at the community site to discuss the study with the patient, and should the patient agree via their health care professional, the researcher will discuss the study with the patient.

Secondary care patients will be identified from diabetes clinics by healthcare professionals and given the invitation packs. Procedures, thereafter, will be the same as in primary care.

Participants may also be recruited via advertisement in the press or posters displayed around the community including supermarkets, community centres, pharmacies, hospitals and GP practices. In addition, the social media may be used to advertise the study including websites, Facebook and Twitter.

It is planned for recruitment to happen over a 15-month period. With the patient's consent, their GP practice and diabetes specialists will be notified of their participation in the research.

2.2.4 Visits

2.2.4.1 Screening and Baseline MeasurementVisit (Visit 1)

Patients expressing an interest in the study will be given an appointment for a screening visit (Visit 1), a researcher will review the patient information sheet with the patient and informed consent will be taken. Signed consent will be obtained from patients. A signed copy of informed consent form (ICF) will be given to the patient for their records, a copy will be sent to their GP and the final copy will be kept with the site file (SF).

Patients will undergo the following measures with suitably qualified members of the research team:

1. Clinical history;
2. Clinical examination including ECG, heart rate and blood pressure;
3. Anthropometric measures and body composition;
4. Screening questionnaires
5. Blood Sample
6. Pregnancy Test

After the screening visit and with review of inclusion/exclusion criteria, patients will be invited to Visit 2. Patients will be provided with questionnaire booklet to either complete or return at Visit 2. Patients will be asked to carry out a 3-day food diary and 3-day blood glucose self-monitoring for review at Visit 2.

If the patient does not fulfil criteria during the screening visit, the patient will be informed and the reasons explained at the screening visit. If blood results taken at screening are the reason for exclusion, the patient will be invited to Visit 2 to discuss the findings and reasons for exclusion.

2.2.4.2 Visit 2

Patients will arrive fasted (appropriate advice regarding insulin intake will be given during visit 1). An intravenous cannula will be placed by a trained member

of the research team and patients will undergo a mixed meal tolerance and appetite study. Patients will be randomised to the intervention or routine care group. Actigraph, Dexcom G4 and ApneaLink equipment to be given. Patients will return completed questionnaire booklets and 3-day food diary and 3-day blood glucose self-monitoring information. Patients will meet the research dietitian and clinician where they will be given specific instructions related to diet and clinical management of their diabetes.

2.2.4.3 Subsequent Visits

There will be a further 9 visits after 1 week (Visit 3), 4 weeks (Visit 4), 8 weeks (Visit 5), 12 weeks (Visit 6), 16 weeks (Visit 7), 20 weeks (Visit 8), 24 weeks (Visit 9), 36 weeks (Visit 10), and 48 weeks (Visit 11). A visit will be arrange at 104 weeks to assess 24-month outcomes. Table 1 shows the assessment and measures at each of these visits. Sessions will be scheduled during the week with as much flexibility to suit the needs of the patient. Patients will be able to book suitable appointments. Patient visits and test duration is summarised in appendix V.

Table 1. **Summary of Measurements Performed During the Study**

Summary of Research Measurements											
Visit:	**Screening (V 1)**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V 10**	**V 11**
Tests											
Anthropometry: Weight	x	x	x	x	x	x	x	x	x	x	x
Anthropometry: Height	x										
Body Composition: Body Fat via Bioelectrical Impedance	x	x	x	x	x	x	x	x	x	x	x
Body Composition: Fat Free Mass	x	x	x	x	x	x	x	x	x	x	x
BMI Calculation	x	x	x	x	x	x	x	x	x	x	x
Waist Circumference	x					x			x		x
Hip Circumference	x					x			x		x
Waist to Hip Ratio Calculation	x					x			x		x
Blood Samples: U+E, FBC, LFT, HbA1c, Fasting Blood Glucose, Fasting Lipid Profile,	x	x				x			x		x

high-sensitivity CRP, C-Peptide											
Mixed Meal Tolerance Test & Appetite Study		x				x					x
HOMA-IR Calculation		x				x			x		x
QUICKI Calculation		x				x			x		x
Urine Sample: Microalbuminuria, Metabolomics	x					x			x		x
Faecal Sample: Microbiome	x					x			x		x
Blood Pressure and Heart rate	x	x				x			x		x
3-Day Self-Monitoring Blood Glucose	x					x			x		x
3-Day Food Diary	x										x
Questionnaires: DEBQ	x					x			x		x
Questionnaires: ESS EQ5D, PSQI, PAID, ADD-QoL		x				x			x		x
Clinical Interviews: Insulin dose reduction & insulin withdrawal, non diabetes medication assessment, healthcare utilisation, hypoglycaemia episodes	x	x	x	x	x	x	x	x	x	x	x
Clinical Interviews: diet interview, adherence to diet and study		x	x	x	x	x	x	x	x	x	x
7-DayAccelerometry : Physical Activity and Sleep Study		x							x		x
Continuous Glucose Monitor (Dexcom G4)		x				x					x
Approximate length of visit:	1.5 hr	6 hr	1 hr	1 hr	1 hr	6 hrs	1 hr	1 hr	6 hrs	1 hr	6 hr

Note: At 24~~18~~ month, the patient and/or~~s~~ GP will be contacted for ~~weight~~anthropometric data, blood and HbA1c results**.**

2.2.5 Telephone Consultations

In addition to the patient visits, patients will have telephone consultations with a member of the research team in-between their clinical assessments. A schedule of telephone consultations is available in appendix V.

2.2.6 Travel Expenses

Patients will be reimbursed reasonable travel expenses for visits up to £5/visit.

2.2.7 Case Report Form (CRF) and Data Collection

Case report form contain source data material like eligibility criteria form, withdrawn criteria form, medical records, patient‘s demographic data, smoking and drinking habits, medical history, questionnaires, clinical interview records, laboratory records, physical measurement records, logs, record books, checklists that will be completed at all patient visits. Patients will be given a participant ID number, which they will be referred to by. All study related records except for the ICF will have the participant ID number and not their name. CRF will be completed by the member of the research team. Data will also be collected at the assessment visits. The data will be forwarded to an electronic database for analysis at the end of trial.

2.3 Intervention

Research Team: includes medical doctors, registered dietitians, research fellows, and PhD research students.

- *Principal Goals:* the primary purpose of this study is to achieve least a 5% weight loss of initial weight following a low calorie diet and physical activity intervention (17). 7-10% weight loss does improve HbA1c, glycaemic response, reduces blood pressure in T2D patients. Patients will be expected to lose 10% body weight with the likelihood that they will at least lose 5% during 6 months. Patients will be randomised to receive either the CWP or routine care for 6 months. Both intervention groups will start receiving the intervention from a research dietitian at Visit 2. The dietitian will describe the intervention to the patient and give the patient ample opportunity to ask any questions they have.

- *Physical Activity:* the patient’s will be advised to improve their fitness levels by engaging in unsupervised physical activity at least 30 min per day 5 days per week, in accordance with physical activity guidelines (18, 19, 20, 21, 22). Higher physical activity levels will be encouraged during the trial for optimal weight loss and weight maintenance (23, 24). There is firm evidence from large cohort studies (25, 26) that higher physical activity bouts on weekly basis have positive effects on weight loss and vascular health. Potential benefits of variation in exercise activities will be pointed out to the patient. Advice will mainly be given regarding

walking. For this reason, those unable to walk due to severe musculoskeletal conditions will be excluded.

2.3.1 Phase I: Months 1 to 6

- *Treatment Design and Frequency*: the patients will attend 9 sessions during the 6-month intervention.

- *Cambridge Weight Plan 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. LCD has been extensively researched (27, 28). This study will use 800 calories as a benchmark (28). For the first 12 weeks, patients will be asked to consume four Cambridge Weight Plan products (meal replacement product; MRP) to make total calories of approximately 800 kilocalories (kcal). The 4 Cambridge Weight Plan products will be nutritionally complete (29). Patients will receive the Cambridge Weight Plan, free of charge, at visits. Participants will be advised to use a fibre supplement (psyllium/inulin) to avoid constipation if required. They will be advised to drink at least 2 litres of water or other energy-free beverages (except tea and coffee) each day (27). Individualised plans of the Cambridge Weight Plan will be followed under the CODEX (30) and DOM UK (31) guidelines over the first 3 month of the intervention period. After the initial 12 weeks, each patient will follow the Cambridge weight programme with reintroduction of conventional foods (reference). This will involve a graded programme of Cambridge pro800 products and conventional foods. Patients will initially increase their calories to approximately 1000 per day (6 weeks). This will involve patients reducing the Cambridge Pro800 to either 3 a day with 400kcal protein rich foods with some skimmed milk; or 2 products a day with 600kcal protein rich food, skimmed milk and fruit. The quantities and weights of the food, skimmed milk and protein will be discussed with the patients. Thereafter they will move to 1200kcal per day (6 weeks) which will involve 2 Cambridge Pro800 products plus 800kcal split between breakfast, lunch and evening meal, skimmed milk and fruit. Patients will go up to a maximum of 1400-1500kcal per day, depending on weight gain calories might vary. In addition the intervention will be looking at long-term lifestyle modifications through an education curriculum which will include goals setting, healthy eating, emotional and conscious eating, slip ups and setbacks and maintenance of

weight loss. The diet regimen will be supervised by a research dietitian or a trained member of the research team (27), and medical doctor.

- *Routine Care Group:* will include scheduled dietetic appointments aiming to improve diet and help in weight loss through lifestyle modification. Patients will receive the same frequency of contact as the CWP group. Patients will be asked to consume a 600 kcal deficit diet (based on their calculated basal metabolic rate, BMR, using the Mifflin St-Jeor equation throughout the intervention (32, 33)). Individualised diet plans will be advised for this group and BMR will be adjusted for weight loss and dietary plans adjusted accordingly. Kcal will come from starchy carbohydrates, protein, unsaturated fats, and vitamins, minerals and trace elements to the UK recommended daily amounts based around guidelines for health eating by the Department of Health and NHS choices. This study will follow the DOM UK (30) guidelines for dietary changes and advice from dietetic intervention within this time. The focus will be on long-term lifestyle modifications through an education curriculum which will include goals setting, healthy eating, emotional and conscious eating, slip ups and setbacks and maintenance of weight loss. The diet regimen will be supervised by a research dietitian or a trained member of the research team (27), and medical doctor.

- *Physical Activity:* patients in both groups will be instructed to spread daily 30 min exercise across the day. Their physical activity will be assessed through a 7-dayaccelerometry worn on the upper arm.

- *Sleep Study:* sleep patterns will be assessed through using a SenseWear (accelerometry); this will be the same device that also measures physical activity. Sleep apnoea will be assessed through an overnight non-invasive home monitoring device currently used in clinical practice (ApneaLink). The Apnealink is a small device, measures nasal airflow and pulse oximetry. The study will be reviewed by members of the research team and a medical doctor and if there is an indication of sleep apnoea requiring treatment (apnoea-hypopnoea index >5 and Epworth Sleepiness Scale >15), the patient and the GP will be informed so that appropriate referrals for treatment are made.

-*Continuous Glucose Monitoring:* Glucose variability will be assessed using a Dexcom G4 (real-time continuous glucose sensor system). The Dexcom G4 system is a CE marked real-time continuous glucose sensor system, which provide dynamic glucose

information to people with diabetes, or their carers. These glucose data are updated every 5 minutes. Sensors last seven days and participants will be instructed on how to remove a sensor and implant a new one. The G4 system sensor requires calibration to capillary blood glucose values twice a day and verification with a capillary blood glucose test before treating diabetes based on sensor reported data. Participants will given the Dexcom G4 sensor with a blinded receiver which stores glucose data but does not make it available to the participant. The participants will wear a Dexcom G4 continuous glucose sensor in the anterior abdominal wall, where the sensor detects glucose in the interstitial fluid and is calibrated to capillary blood glucose values taken a minimum of twice daily. Participants will attend the clinical research facility 2 weeks after randomisation and at visit 6 and 11 and data will be downloaded from their CGM device.

- *One-to-one consultations:* Initial consultations will last 45 minutes and include a weight history, previous weight loss attempts, goals setting and barrier to change. All subsequent visits will involve 30 min sessions with a dietitian or a trained member of the research team followed by 30 min session with a medical doctor or a member of the research team.

A skilled research dietitian will assess patient adherence to the diet, discuss any concerns they may have regarding the diet and physical activity. Patients will also be weighed at these consultations. Patients who are experiencing difficulties in adhering to the diet and/or are not able to sustain the physical activity guidelines will receive guidance and help in solving these issues. Emphasis will be on goal setting and lifestyle changes. Patients will be encouraged to keep a food and mood diary throughout the study duration. Which excludes the two, 3-day food diaries. This is to aid patient to become to more conscious about their eating and will be used to assess changing behaviour to the advice.
The medical doctor will assess the impact of the intervention on diabetes medication. Medical advice will be given during the consultation and any clinically necessary investigations carried out.
Patients will have the opportunity to reach the research team on a daily basis through email and telephone during the 6-month intervention phase.

2.3.2 Phase II: Months 7 to 12 – The Follow Up

- *Treatment Design and Frequency*: following the end of the intervention period, patients in both groups will be followed up for a further 6 months to assess endurance of the effects of the intervention. Clinical assessments will take place at 9 months and 12 months. The follow up phase is crucial for weight maintenance because frequent contact with the patients allow monitoring of progress. According to Ulen et al. 280) studies have shown that frequent consultation has a positive effect on weight maintenance. Patients will have the opportunity to reach the research team on daily basis through email and telephone during the 12-month intervention phase. A further clinical assessment will be scheduled at 24 months to assess the maintenance of change following 12-month intervention.

- *Diet Intervention:* both groups will receive the same guidelines during the follow up period. Patients will be advised to follow the 600 kcal deficit diet from conventional foods and continue with the educational curriculum to aid long term maintenance. BMR will be calculated and appropriate individualised diet plans will be advised and BMR will be adjusted for weight loss (1kg or 2.2lbs per week) and dietary plans adjusted accordingly to prevent weight regain. Patients will receive follow up dietary advice from a skilled dietitian or a trained member of the research team.

- *Physical Activity:* patients will be advised to sustain their physical activity levels.

- *One-to-one consultations:* will involve up to 60 min consultations (up to 30 min with a skilled dietitian or a trained member of the research team followed by up to 30 min with a medical doctor).

The dietitian or a trained member of the research team will assess the patient's adherence to diet and physical activity. Dietary and physical activity adherence will be assessed at the follow up visits. The dietitian or a trained member of the research team will also weigh the patients during the consultations.

The doctor will assess the state of their participant's diabetes medication.

2.3.3 Concomitant Medication

Patients will use insulin, statins, and renoprotective medications as part of their treatment because it meets the inclusion criteria and is necessary as suitable supportive care at the beginning of the intervention until the research team can establish that the patients can

safely reduce the dosages and/or eliminate the drugs. Patients will be asked to avoid over-the-counter medications, nutritional supplements, and not to take additional non-pharmacologic medication during the study unless it is agreed by the investigative team. Any medication, other than the ones prescribed or recommended by the clinicians in the study will also be recorded in the CRF.

2.3.4 Insulin Titration

Patient's insulin will be managed by their diabetes specialist nurse and/or medical doctor. The dose will be adjusted throughout the study and the patient's glucose levels will be frequently measured. Throughout the visits, the patient's weight loss and glycaemic control will be assessed. Adjustment to diabetes medications will be made according to protocol aiming to reduce doses.

Patients will have frequent contact with the medical doctor to assess their progress and receive advice on how to adjust the insulin medication at these visits. Routine care patients will receive similar medication adjustment guidelines and frequency of contact from the research team as the Cambridge Weight Plan group. Insulin adjustment algorithm is available. .

2.3.5 Meal Tolerance Test and Appetite Test

Patients will have a meal tolerance test to measure area under the curve C-peptide (AUC CP), which is the gold-standard measure of endogenous insulin secretion. The protocol is available in appendix VI.

2.3.6 Accountability for the Cambridge Weight Plan

Cambridge Manufacturing Company Limited UK will supply the Cambridge Weight Plan products. The chief investigator (CI) will authorise usage of standard prescription form to order the Cambridge Weight Plan and the member of the research team will collect the Cambridge Weight Plan products. Unused products will be retrieved by the dietitian at the end of the study.

2.3.7 Patient Adherence

The patient will be instructed to return all unused or part-used Cambridge Weight Plan products at each visit. The study investigators may withdraw patients from the study if their adherence is unsatisfactory.

2.3.8 7 Post Trial Treatment

Patients will transfer to normal care and continue to be cared for by their GP or specialist diabetes team. The patients will be asked to follow a 600 kcal deficit diet to help maintain their weight and weight maintenance will be discussed.

2.4 Outcome Measures

The primary outcome in this study is weight loss. The secondary outcomes include body composition, diabetes control, insulin use, glucose variability, other diabetes medications, beta-cell function, to determine effect on hunger and appetite, cardiovascular risk factors, and quality of life. Standing operating procedures (SOP;) are developed to ensure that the trial meets the relevant standards.

2.4.1 Research Measurements

A series of measurements performed at all visits are summarised in Table 1..

2.4.2 Telephone Consultations

Telephone consultations will be scheduled during the week to allow for as much flexibility as possible to suit the needs of the patient. A member of the research team will ask each patient to identify slots (days and times) that would be most suitable for them. Patients will have a clinical assessment, assess their adherence to the dietary changes and identify any issues they are having with compliance or adverse events. Telephone consultations will last up to 15 minutes and a summary of telephone consultation will be attached to the CRF. There are no risks involved in this procedure.

2.4.3 Follow-up Visits

The follow up visits will involve one-to-one consultations interviews summarised in Table 1. Patients will visit the site for follow up at 9 month and 12 month. A further clinical assessment will be scheduled at 24 months to assess the maintenance of change following 12-month intervention.

2.5 Sample Size

The standard deviation of the baseline weights is estimated to be 15 kg, based on Christensen et al. (29). The clinically important difference that the study is designed to detect is 10 kg. At the 5% significance level and with 80% power that requires a sample size of 74 (37 per arm), based on a standard t-test. The dropout rate of 20% is estimated to be, which increase the sample size to 90. However, when using the ANCOVA method the sample size is affected by the correlation between the before and after measurements, as shown in Borm et al. (34). This study has been unable to find an estimate of this correlation but if assumes it to be 0.5, the sample size required would be 67. This is indication only; the sample size will be 90.

2.6 Randomisation

Randomisation will be carried out using an online software randomisation package (Sealed Envelope), Investigators randomise patients by simply completing an on-screen form with patient details, inclusion and exclusion criteria. Investigators are immediately shown the treatment allocation (35).

2.7 Blinding

Neither the patients nor the investigative team will be blinded to the intervention arms as blinding will not be possible (36). Data analysis, however, will be blinded.

2.8 Statistical methods

The primary outcome is weight loss at12 months. This will be assessed using an ANCOVA model. The response variable will be weight at twelve months. The covariates will be weight at baseline and a binary variable indicating whether the participant was in the intervention group or the control group. The regression coefficient of the group term represents the effect size of the intervention. In addition to this main, unadjusted analysis and adjusted analysis will also be performed by adding the following covariates into the model; weight, body fat, fat free mass, HbA1c, HOMA-IR, QUICKI and insulin medication. The primary analysis will be done using the intention-to-treat method. Secondary outcomes will be analysed in the same way, using unadjusted and adjusted analyses, under the intention-to-treat principle. All outcome measures will also be analysed with per protocol. Continuous measures will be analysed using an ANCOVA model, with the baseline measure of the outcome as a covariate. If the distribution of the outcome is not a normal distribution then appropriate transformations will be performed.

3. Results

3.1 Participation flow

The study's patient flow diagram is available in appendix VII.

3.2 Study period and recruitment

This research will commence in September 2014. Since previous approval, no contact has been made with the patients regarding recruitment.

3.3 Baseline data

Table 2. **Baseline Characteristics of the Patients in the Intervention and Control Group**

Characteristics	**Intervention Group (N =)**	**Control Group (N =)**
Sex (no.)		
-Male		
-Female		
Age (yrs)		
Height (cm)		
Weight (kg)		
Ethnicity		
Body mass index (kg/m²)		
Hip circumference (cm)		
Neck circumference (cm)		
Waist to hip ratio		
Body fat (%)		
Fat free mass (%)		
HbA1c (%)		
On Insulin (%)		
Insulin (pmol/l)		
Other medications		
Duration of Diabetes		
Urinary ACR (mg/mmol)		
Metabolomics		
Microbiome		
Fasting Plasma glucose (mmol/l)		
-Blood		
Blood pressure (mmHg)		
-Systolic		
-Diastolic		
Pulse Rate		
Fasting Serum lipids (mmol/l)		
-Total cholesterol		

-HDL cholesterol -LDL cholesterol -TriglyceridesHOMA-IR QUICKI High-sensitivity C-reactive protein (CRP, measured in mg/L)

3.4. Side Effects and Adverse Events

The Cambridge Weight Plan has shown a good safety profile in several studies. The common side effects reported with the Cambridge Weight Plan include: dehydration, diarrhoea, constipation, headaches, nausea, mild dizziness, electrolyte imbalance, Gout, mild ketosis, and getting less sleep.

3.2 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event(SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** *–refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

3.3 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

3.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

3.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e resulted from the administration of any of the research procedures; and
- 'unexpected', i.e an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs –

Fax: 02083838320, attention Professor Gary Frost

Please send SAE forms to: Professor Gary Frost, Division of Diabetes, Endocrinology and Metabolism, 6th Floor Commonwealth Building, Faculty of Medicine, Imperial College Hammersmith Campus, DuCane Road, London, W12 0NN

Tel: 02883838037(Mon to Fri 09.00 – 17.00)

3.5 Definition of End of Trial

The end of trial is the date of last patient's visit. The timeline of the trial is available.. At this point, the patient will receive a personal letter of thanks from the research team (appendix VIII). The practice will receive a letter of thanks from the research team as well (appendix IX).

4. Ethics

4.1 Declaration of Helsinki

This study will be carried out in accordance with the principles of the Declaration of Helsinki.

4.2 Research Governance and Quality Control

The Study will be sponsored by the Imperial College London. This study will comply with the International Conference of Harmonisation Good Clinical Practice ICH GCP (CPMP/ICH/135/95) July 1996, relevant regulations and SOP.

4.3 Trial Registration

This study trial has been registered with ISRCTN and we have obtained an approval number.

4.4 Protocol Publication

The electronic version of the study protocol will be available online at the trialsjournal.com.

4.5 Confidentiality

The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. The investigative team will maintain the patients anonymity. All patient data will be anonymised with a patient ID number except for the ICF, which will have the patients name and initials on. Only authorised personnel will have access to the study documents and only anonymised data will be entered by the investigative team into the secure computerised databases. Access to the secure computerised databases will be restricted only to the investigative team.

4.6 Data Storage

All data and documents will be stored safely in locked cabinets at the original study site.

5. Funding

This trial is funded by the Cambridge Manufacturing Company Limited, UK. The funders will have no further role in the study.

6. Indemnity

- *Negligent and Non-Negligent Harm:* Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

7. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8. Research Findings

8.1 Public Engagement

At the end of the study, a newsletter will be sent to all patients highlighting, in lay terms, the main findings of the study. The CI will also be happy to speak to local support groups and GP surgeries and engage the public with the specific findings of this study.

8.2 Dissemination of Findings

Anonymised study results will be presented at relevant conferences and symposiums (e.g. UK Nutrition Society annual meetings) as a means of early communication. Full reports and papers will then be prepared for publication in high impact medical, nutrition, and diabetes related journals (e.g. British Medical Journal, British Journal of Nutrition, Diabetes, and American Journal of Clinical Nutrition). The reports and papers that are published about the research will not identify patients who participated in this study.

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