eDIAMOND
Dietary approaches to the management of type 2 diabetes

PROTOCOL

Study Title: The effectiveness of a low-carbohydrate, low-energy diet with remote support for patients with type 2 diabetes in primary care on weight loss: a proof of concept (PoC) trial

Internal Reference Number / Short title: eDIAMOND PoC Study

Ethics Ref: 23/EE/0278

IRAS Project ID: 323582

Date and Version No: V1.2 03/01/24

Chief Investigator: Dr Nicola Guess
Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre; Nicola.Guess@phc.ox.ac.uk

Investigators: Professor Paul Aveyard
Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre
Professor Susan Jebb
Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre
Dr Elizabeth Morris
Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre
Dr Sarah Wane
Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre
Dr Garry Tan
Consultant Diabetologist and the Clinical Lead at the Oxford Centre for Diabetes, Endocrinology and Metabolism

Sponsor: University of Oxford

Funder: This work is supported by the NIHR Programme Grant for Applied Research (PGfAR) for NewDAWN.

Chief Investigator Signature:

All the investigators declare that they have no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. KEY CONTACTS

Chief Investigator	Dr Nicola Guess Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG. Email: Nicola.Guess@phc.ox.ac.uk Telephone: 07951 252395
Sponsor	University of Oxford Research Governance, Ethics & Assurance Team Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB. Email: RGEA.Sponsor@admin.ox.ac.uk
Funder(s)	This work is supported by the NIHR Programme grant for Applied Research for NewDAWN.
Committees	Trial Management Group: Dr Nicola Guess, Professor Paul Aveyard, Professor Susan Jebb, Dr Elizabeth Morris, Dr Sarah Wane (Trial Manager), two lay members.

2. LAY SUMMARY

Type 2 diabetes (T2D) can be put into remission (achieving normal or near-normal blood glucose levels without medications) if treated with intensive weight loss support. Currently available evidence is that a very low-energy diet (about 800-900kcal per day) delivered using meal replacement products is the most effective way of achieving remission in primary care. However, about 75% of people offered a meal replacement programme turn it down, and low-carbohydrate low-energy diets could be an attractive alternative for many. Researchers at the University of Oxford developed a face-to-face low-carbohydrate, low-energy diet (DIAMOND) programme which achieved on average almost 10kg weight loss and normalisation of blood glucose in a 12-week feasibility study, and has now been taken to full trial.

The patients and healthcare professionals who took part in the DIAMOND study were keen to know whether the same results could be achieved using this dietary approach but when the behavioural component is provided through digital tools and remote support as an alternative to face-to-face appointments with a practice nurse. This has the potential for more frequent support without increasing the demand on the primary care workforce. Remotely-delivered interventions also offer more flexibility for the patient, without the need to attend a GP practice or physical location at a particular time. If effective, remote interventions could increase access and choice for patients who are keen to take part in a weight loss or remission programme. Encouraging data from other weight loss programmes show that a remote version can work just as well as a face-to-face version. Nevertheless, we want to test whether a

remote intervention of DIAMOND can achieve similar weight loss results as seen in the face-to-face version before rolling it out at scale.

Therefore, this proof of concept study aims to assess whether a remotely delivered behavioural support programme helps people follow a low-carbohydrate, low-energy diet (eDIAMOND) achieves clinically significant weight loss compared with no support or dietary advice.

3. SYNOPSIS

Study Title	The effectiveness of a low-carbohydrate, low-energy diet with remote support for patients with type 2 diabetes in primary care on weight loss: a proof of concept (PoC) trial		
Internal ref. no. / short title	eDIAMOND PoC Study		
Study registration	Clinicaltrials.gov: TBC		
Sponsor	University of Oxford		
Funder	NIHR Programme Grant for Applied Research		
Study Design	Randomised controlled trial		
Study Participants	Adult men and women with type 2 diabetes and BMI over 27 kg/m^2 (where individuals are from White ethnic groups) or over 25 kg/m^2 (where individuals are from Black, Asian and other ethnic groups)		
Sample Size	60 in total – allocated in a 1:1 intervention: control ratio Recruited from 5 GP practices in England.		
Planned Study Period	From 01/01/2024 to 30/06/2025. In total 18 months (Each participant will be followed up for 5 months).		
Planned Recruitment period	08/01/24 – 31/10/24		
	Objectives	**Outcome Measures**	**Timepoint(s)**
Primary	To test the effect of the intervention on weight loss compared to standard NHS care.	Change in weight	**Week 20**
Secondary	To assess the potential effectiveness of the eDIAMOND intervention to reduce CVD risk compared to standard NHS care.	Change in HbA1c Number of participants with HbA1c <48mmol/L on no medications Change in diabetic medication (number of diabetic medications;	**Week 20** **Week 20** **Week 20**

		change in anti-glycaemic medication effect score)	
		Change in total cholesterol, LDL-cholesterol, total cholesterol:HDL ratio, triglycerides	**Week 20**
		Change in BP (systolic, diastolic)	**Week 20**
	To compare the effect of the intervention vs NHS standard care on quality of life	Change in antihypertensive medication (number of medications	**Week 20**
	To investigate whether the intervention is feasible to deliver should we take the project full trial	Change in patient's wellbeing (WHO 5), problem areas in diabetes (PAID) score	**Week 20**
		Percentage of people who fulfil the recruitment criteria who accept the invitation to participate	**Baseline**
		Participant adherence to the protocol assessed by self-reported carbohydrate intake measured using an online food intake questionnaire	**Week 20**
	To explore the experience of the intervention for participants and impact of the programme on participants' lives and behaviour	To see whether the control group may have also changed their carbohydrate intake (contamination), measured by self-reported carbohydrate intake measured using an online food intake questionnaire	**Week 20**
		Telephone interviews with participants and online questionnaire	**Week 20**

4. ABBREVIATIONS

BP	Blood pressure
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trial Unit
CVD	Cardiovascular disease
DPA	Data Protection Act
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HbA1c	Glycosylated Haemoglobin A1c
HRA	Health Research Authority
ICF	Informed Consent Form
IG	Information Governance
INR	International Normalised Ratio
NHS	National Health Service
NIHR	National Institute for Health and Care Research
RES	Research Ethics Service
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
T2D	Type 2 diabetes mellitus

5. BACKGROUND AND RATIONALE

There are over 4.5 million people living with type 2 diabetes (T2D) in the UK, with numbers expected to rise to 5.5 million by 2030 (1). Currently, 10% of the NHS annual budget is spent on diabetes (around £10 billion).

But the paradigm for T2D management is changing (2) What was previously thought to be a lifelong progressive condition to be managed primarily with escalating doses of medications, may instead be put into remission if treated with intensive weight loss support (3). There is considerable uncertainty regarding the optimal diet composition for weight loss for people with T2D, but there is a growing interest from patients and practitioners in using low carbohydrate diets to achieve weight loss (4, 5), improve glycaemic control and achieve disease remission.

In our previous DIAMOND study (6), a randomised controlled feasibility trial (n=33), we demonstrated that it was feasible and acceptable for practice nurses to support patients with T2D to adopt a low-carbohydrate, low-energy diet in primary care (7). On average, participants in the intervention group achieved clinically significant improvements in weight and HbA1c in the short-term (12 weeks)(7). Participants received no further formal support or intervention after the 12-week period. In qualitative interviews after the study completion, healthcare professionals and participants expressed an interest in whether the programme could be expanded to include app-based or other remote support. Patients were keen to consider increased levels and modes of support, and the potential for a synchronous "community" of participants to support each other. Practitioners were concerned about adequate workforce capacity and time constraints of delivering increased face-to-face contacts within primary care.

Remotely delivered interventions also offer more flexibility for the patient, without the need to attend a GP practice or physical location at a particular time. Therefore, remote interventions can increase access and choice for patients who are keen to take part in a weight loss or remission programme (8). Encouraging data from the NHS Diabetes Prevention Programme (9) and the digital NHS Low Calorie Diet Programme (unpublished data) provides some reassurance that face-to-face interventions can be delivered remotely without any unacceptable reduction in effectiveness and may improve access for some patients. Nevertheless, it is important to test whether uptake and effectiveness of a newly developed remote intervention can achieve comparable outcomes as seen in the face-to-face version.

Previous work by our study team has established that we can successfully recruit to a variety of dietary interventions (such as DROPLET, DIAMOND), and have sufficient participants completing the intervention such that we can collect full follow-up outcomes. However, in a previous pilot attempt to adapt an "in person" low-carbohydrate intervention to a remote intervention was not successful because people did not lose weight. We think this was because people did not understand that they needed to cut carbohydrate quite significantly. This is important because weight loss is what drives remission of T2D. This is why we have chosen weight loss as the primary outcome for this study, and why we will also assess carbohydrate intake as a secondary outcome.

Therefore, the aim of this study is to test in a proof of concept (PoC) randomised controlled trial whether the DIAMOND programme, modified to be delivered remotely, is effective at achieving clinically significant weight loss in people with T2D.

Understanding changes in clinical outcome measures and participant behaviours could inform future programmes to support people with type 2 diabetes in primary care.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	Timepoint(s)
Primary	To test the effect of the intervention on weight loss compared to standard NHS care.	Change in weight	**Week 20**
Secondary	To assess the potential effectiveness of the eDIAMOND intervention to reduce CVD risk compared to standard NHS care.	Change in HbA1c	**Week 20**
		Number of participants with HbA1c <48mmol/L on no medications	**Week 20**
		Change in diabetic medication (number of diabetic medications; change in anti-glycaemic medication effect score)	**Week 20**
		Change in total cholesterol, LDL-cholesterol, total cholesterol:HDL ratio, triglycerides	**Week 20**
		Change in BP (systolic, diastolic)	**Week 20**
		Change in antihypertensive medication (number of medications	**Week 20**
	To compare the effect of the intervention vs NHS standard care on quality of life	Change in patient's wellbeing (WHO 5), problem areas in diabetes (PAID) score	**Week 20**
	To investigate whether the intervention is feasible to deliver should we take the project full trial	Percentage of people who fulfil the recruitment criteria who accept the invitation to participate	**Baseline**
		Participant adherence to the protocol assessed by self-reported carbohydrate intake measured using an online food intake questionnaire	**Week 20**
		To see whether the control group may have also changed their carbohydrate intake (contamination), measured by self-reported carbohydrate intake measured using an online food intake questionnaire	**Week 20**
	To explore the experience of the intervention for participants		**Week 20**

	and impact of the programme on participants' lives and behaviour	Telephone interviews with participants and online questionnaire	

7. STUDY DESIGN

This proof of concept trial will be an individually randomised controlled trial, performed in adult patients with type 2 diabetes and a BMI over 27 kg/m^2 (where individuals are from White ethnic groups) or over 25 kg/m^2 (where individuals are from Black, Asian and other ethnic groups). Participants will be randomly assigned to either the intervention group (eDIAMOND programme) or the control group (NHS usual care). 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.

Briefly, the eDIAMOND programme will consist in a low-carbohydrate, low-energy diet intervention which will be 12 weeks of support for weight loss, and 8 weeks of weight maintenance support. Online support from health coaches will be available throughout the programme.

All participants from both groups will be enrolled for 5 months from randomisation to final follow up. Data collection will be in the form of clinical and biochemical measurements (Weight, HbA1c, cholesterol). A schematic of the study is included in appendix A.

This is an individually randomised controlled trial. Participants will be recruited via GP practices and randomised 1:1 with simple randomisation, stratified by T2D duration (≥/< 6 years), to either the intervention group or control (usual care). They will be enrolled in the study for 5 months. Most study procedures will be conducted online or remotely by telephone or via video calls by Microsoft Teams/Zoom if participant prefers. If by Microsoft Teams/Zoom, the coach will call the participant at the time of the appointment and the coach and participant will be able to talk and see each other via the camera (if participant prefers)) including: screening, eligibility assessment, informed consent, randomisation, engagement with the remote intervention. Participants will be asked to attend 2 face to face appointments for the research study at their local GP practice for measurements to be taken (weight, blood pressure) and blood tests, at baseline and 20 weeks (5 months) post randomisation. Face to face appointments will be incorporated with routine clinical appointments when possible.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

This study will include 60 adult participants from 18 to 65 years old, with type 2 diabetes and BMI equal to or over 27 kg/m^2 (where individuals are from White ethnic groups) or equal to or over 25 kg/m^2 (where individuals are from Black, Asian and other ethnic groups) who would consider (or prefer) using dietary means to achieve weight loss and improve diabetic control.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18 – 65 years.
- BMI equal to or over 27kg/m^2 (where individuals are from White ethnic groups) or equal to or over 25kg/m^2 (where individuals are from Black, Asian and other ethnic groups)
- Diagnosed with type 2 diabetes
- Must have good IT skills (they can use a computer/smart phone)
- Must complete baseline assessments

The participant may not enter the study if ANY of the following apply:

8.3. Exclusion Criteria

- Currently diagnosed with type 2 diabetes but who are in remission using the NHS diabetes remission criteria, or who are recorded as not on diabetes medication and whose HbA1c levels on enrolment are <48mmol/mol at baseline
- Currently using insulin injections
- GLP1-agonists or SGLT2 inhibitors started in the six months prior to study enrolment
- Diagnosed with a known eating disorder for whom the programme could be unsafe or require extensive monitoring to ensure safety
- People who are pregnant or planning pregnancy
- People who are breast feeding
- Diagnosed with a myocardial infarction or stroke in the past three months, or uncontrolled cardiac conduction abnormalities e.g. long QT syndrome.
- Currently diagnosed with maculopathy or proliferative retinopathy
- People with HbA1c ≥87mmol/mol
- People with significant life-limiting illnesses that mean that remission is unlikely to improve health (severe cardiac failure, palliatively treated cancer, dementia), or other current severe illness
- Planned major surgery that means that following a weight loss programme would not be possible.
- People taking part in other research that would compromise either their participation in eDIAMOND or the other research study/ies that they are participating in.
- Taking part in or planning to take part in the NHS Pathway to Remission programme.

NB: If the patient is taking warfarin, they are not excluded from participating in the study, but will be advised to inform their local monitoring service about their participation, and they may be advised to have additional blood test monitoring of their INR as part of their care.

9. PROTOCOL PROCEDURES

9.1. Recruitment

60 patients will be recruited from 5 GP practices from the NIHR CRN Thames Valley and South Midlands. The primary care provider will search their electronic registers for eligible individuals and GPs will screen out those to whom it would be inappropriate to invite to participate. The GP will send a letter/email/text/phone (this will depend on the GP preferences) to invite the patient to consider taking part in the study. The letter/text/phone call will direct the patient to the study website where they will be able to access the online Participant Information Sheet. Contact details for the research team will also be available for participants to discuss the study in more detail and/or ask any questions.

Participants wishing to be considered for inclusion in the trial will be directed to the section of the website to complete the initial eligibility assessment. This helps to ensure participants have sufficient IT skills to be able to engage with the intervention.

9.2. Screening and Eligibility Assessment

As part of the initial eligibility assessment all potential participants will be asked to report their height and weight to calculate BMI (these numbers will not be recorded, just whether they meet eligibility criteria or not). If the participant is ineligible a pop-up will explain that they do not meet the eligibility criteria for this study and they will not proceed further, and no information will be requested. If they are eligible they will be asked to provide their full name and email via an approved secure platform (the RedCAP programming system, run by the University of Oxford Nuffield Department of Primary Care Health Sciences Clinical Trials Unit, where the information will be stored securely and in compliance with local IG policy) so that the research team can contact them. The PIS will be downloadable from the website, however there will also be a note on the study website that if desired a paper copy of the PIS can be sent to the participants.

9.3. Informed Consent

As detailed above (section 9.1) potential participants will visit the study website to read the Participant Information Sheet online and will be able to print it out if they wish to, or be sent a hard copy by the study team on request. The Participant Information Sheet and Informed Consent presented to the participants online will detail no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The potential participant will be allowed as much time as they wish to consider the information and have the opportunity to call the research team, their GP or consult other independent parties to ask any questions before they decide whether they will participate in the study. Following their initial eligibility assessment (section 9.2), eligible participants will be provided with a link via email or text to the online database where consent is taken. Once the informed consent CRF is completed, participants will have the option to download a copy of their consent form for their records. They will then be able to

complete the online baseline assessment by following a link displayed once informed consent has been confirmed (defined as all sections of the informed consent CRF being appropriately completed).

Participants will be able to download a copy of the signed consent form to keep for their records. A pdf copy of the signed consent form will be kept with the participant's medical notes and another copy will be retained at the research site in within the database.

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Prior to the start of the baseline appointment, the clinician will ensure that the participant has read the participant information sheet, and has confirmed that the participant has understood all elements in the consent form, including study requirements and withdrawal policy. The clinician will be approved by the PI at the site to be able to take consent. Once they are satisfied that the participant has given fully informed consent, they will be able to proceed with the baseline appointment.

9.4. Baseline Assessments

All participants from both groups (intervention and control) will complete a 2-part baseline assessment, firstly online and then at their GP practice.

9.4.1. Online:

Participants will be asked to complete a baseline questionnaire requesting demographic information and their current medication, and the standard questionnaires that will be used in the study (the Problem Areas in Diabetes (PAID) score, the WHO 5 (quality of life assessment), and a food intake questionnaire ("Oxford WebQ Questionnaire", where participants are asked to record all food and drink intake in the last 24 hours (10)). This questionnaire will also further assess whether people are willing to complete online trial procedures, and only those who complete all three questionnaires will be randomised. Participants will be informed in the Participant Information Sheet that they will only be able to enter the study after completing each individual questionnaire fully in one attempt as the system will not allow them to go back into each questionnaire to answer the remaining questions later. There are four questionnaires for each participant to complete and should take less than 35 minutes in total. Patients will be able to fill in the baseline questionnaires at any time after completion of the online consent form but before the appointment at their GP practice, as long as they complete each questionnaire in one attempt. Should a participant not complete their questionnaires, reminder emails will be sent at one and two weeks after they received the initial invite to complete the questionnaires.

9.4.2. At the GP practice:

Having completed the online assessment, participant details will be passed to the GP practice (or practice representative in the clinical research network) to book the in-person component of their baseline assessment at their GP practice for measures which cannot be conducted online. At this appointment (with a clinical research network nurse, practice nurse or healthcare assistant), their height, weight and blood pressure will be measured and recorded, and a blood sample taken (approx. 9 ml) for baseline values (HbA1c, blood pressure, total cholesterol, LDL-cholesterol, HDL). Once these results are returned, they will be entered into the CRF. Participants who are recorded as not on diabetes medication and whose HbA1c

on enrolment is <48mmol/mol at baseline will not be eligible for the trial. Similarly, if baseline measures (e.g. BMI) collected at this visit indicate the participant does not meet the eligibility criteria, they will not be randomised to the trial.

9.5. Randomisation and blinding

Once their practice confirms they have attended the baseline appointment, and the participant is confirmed eligible, they will be individually randomised to one of two arms: Intervention (low-carbohydrate, low-energy remote dietary support: 12-week active weight loss phase followed by 8-week weight maintenance phase), or control (usual care; no active additional intervention) stratified by duration of diabetes (≥/< 6 years) using random permuted blocks. The randomisation will be conducted using the Sortition inbuilt randomisation software. This ensures full allocation concealment as information on future allocations is not accessible to the person randomising.

The participants will be aware that they will be randomised to either the remote programme or control, therefore no blinding can take place. Due to the nature of the intervention, it will not be possible to blind members of the study team to participant allocation. An email will be provided to the participant's GP to inform them of which group the participant has been allocated to. Outcome assessment will inevitably be unblinded as patients are likely to tell the nurse. However, the key outcomes are objective measures (weight, HbA1c and medication usage) and the clinicians completing the outcome assessments will not have training or knowledge of the intervention content.

10. Description of study intervention and comparator

10.1. Intervention group (eDIAMOND)

Participants randomised to the intervention group will receive an email informing them they have been assigned to the intervention group, and that their contact information (name, phone number and email) has been securely passed to the eDIAMOND provider (Reed Wellbeing) who will contact them via email or phone (depending on the participant preferences) to process the programme onboarding and account creation. Reed Wellbeing are commissioned by the NHS to deliver weight loss and diabetes education programmes and the staff that deliver the remote coaching have a Level 3 qualification in health improvement/nutrition or similar, and have received additional training in behaviour change from Reed Wellbeing in addition to a half-day workshop on how to deliver eDIAMOND by the study team. The provider will contact the participant with information how to find and access the remote intervention which will be on a webpage. The provider will attempt to contact the participant on 3 occasions and if there is no response this would be flagged to the GP and the GP will be asked to make contact.

Participants randomised to the intervention group will receive the online support from the new programme (eDIAMOND) as well as their standard NHS diabetes care.

The intervention will involve diet, activity and behaviour change components based on key effective dietary and behaviour change components of the original DIAMOND programme. The interventions are designed to adhere to the following standards:

- The core principles are:
    - advice to exclude sugary and starchy foods high in carbohydrates (eg, biscuits, confectionery, bread, pasta, potatoes) entirely from their diet (with the exception of dairy and limited fruit intake).
    - Strict portion control and avoiding energy-dense foods.
    - Standardised 'healthy eating' advice regarding fresh vegetables, and lean meat and fish, is also included.
- Dietary specifications:
    - 800-900kcal per day during the weight loss phase.
    - <26%kcal from carbohydrates during the weight loss phase – some flexibility allowed during weight maintenance to encourage long-term adherence but encourage aiming for lower carbohydrate and higher protein for satiety and weight maintenance.
    - Encourage focus on lean high protein foods and non-starchy vegetables to replace carbohydrate.
- The behaviour change component will include elements of:
    - Goal setting
    - Self-monitoring
    - Peer support

Self-monitoring will be supported by provision of blood pressure and blood glucose monitors for participants to use at home throughout the intervention period. The blood pressure and blood glucose monitors will be sent out via post to participants in the intervention arm following randomisation. These monitors form a key tool for participants to learn and monitor how their weight and diet affect their blood glucose and blood pressure, and will assist their clinicians in assessing their response to the programme and any medication changes. Participants will be given access to a set of instructions as part of the online materials (appendix B) (signposted to by the programme coach) and a printed copy of these sent with the equipment via post, which detail how to use the monitors, and how to interpret the readings should they be unexpectedly high or low, with a traffic light system detailing what action they should take and when they should contact their clinician. Participants will be encouraged to monitor their blood pressure 3 times per week, their blood glucose three times per week (twice a day on these days – once on waking, and once after they have eaten a meal), and to weigh themselves once a week. The coach will ask about the blood pressure, glucose and weight measures during the coaching sessions and these will form a key part of motivating and guiding participants with the intervention.

The programme will include remote coaching sessions at baseline, 2, 4, 8, 12, 16 and 20 weeks to provide support and guidance to the patient to enable them to follow the low-carbohydrate, low-energy intervention (Intervention content shown in appendix B). The participant will receive a text or phone call (depending on the method of contact the participant requests) to organise and schedule the first baseline appointment. All subsequent appointments will be remote and will also be arranged between participants and coach at a day and time convenient for both. In addition, the intervention providers are able to provide additional functionality within their digital offering including access to educational materials, recipe and cooking guides etc (Appendix B). All sessions will be audio-recorded.

Participants randomised to the intervention group will also receive 1 additional telephone appointment with their GP or practice nurse, towards the start of the 12-week intervention period, to review their current medications and assess any changes to their medication regime may be warranted in view of their anticipated participation in the programme and planned weight loss. We will encourage clinicians to do their best to make contact with participants, as this is an important patient contact – they will follow their usual practice protocols for this but we will encourage them to use at least two different methods of attempted contact out of texting, calling, emailing and writing to the patients, and on at least 3 separate occasions. We will provide clinicians with current best practice guidelines they may wish to consider but the decisions for individual patients will remain with their clinician.

For participants in the intervention group, data on participant engagement with the intervention website will be received from the company, Reed Wellbeing, and entered into the database under appropriate agreements.

Clinical responsibility for the participants will remain with the GP at all times. The GP will have access to the eCRF where the hub coach will enter session data, which will include recordings of glucose and blood pressure readings. Furthermore, the eCRF prompts the hub coach to instruct the participant on appropriate action depending on their results, which can include immediately contact the GP practice. In addition, there will be two-way communication between the hub coach and the GP practice. If any information arises in the session where hub coach deems it necessary to inform the GP, they will have details to contact the GP. The participant will be made aware that the GP is able to review any details entered and will be contacted should the need arise.

Reed Wellbeing will retain participant data for up to 12 months after participant completion of the intervention. This is to allow all data to be collected and transferred to the study team for analysis. Reed Wellbeing will not complete analysis on any participant data, and will not be permitted to use this data for any purpose outside of the trial.

10.2 Control group (NHS usual care)

Participants randomised to the control group will receive no additional intervention, and will continue to receive their usual NHS diabetes care from their general practice

10.3 Follow-Up Assessments

10.3.1 12 week-assessment

At 12 weeks after randomisation, all participants from both groups will be sent a link either via email or text to complete a food intake questionnaire.

10.3.2 20 week assessment

At 20 weeks after randomisation, all participants from both groups will also return to their GP practice for measurement of weight and blood pressure, and a blood sample will be taken (approximately 9mls) for measuring HbA1c and lipid profile (total cholesterol, LDL-cholesterol, HDL, triglycerides). To organise this visit, the participant will receive an email, text or phone call. Participants will be able to keep the blood

pressure and glucose monitors. However, if they wish to continue using the glucose monitors, they will need to purchase their own strips. If they don't wish to keep the monitors they can return them to their GP practice at their next study appointment.

At 20 weeks after randomisation, all participants from both groups will be asked by text, phone or email to complete the same questionnaires that were completed at baseline, namely: Problem Areas in Diabetes (PAID) score and the WHO 5 (quality of life assessment). They will also complete the final food intake questionnaire.

Participants in the intervention group will also be asked to complete an online questionnaire about their experience of the intervention. This questionnaire will be sent to participants via an email link to complete at home.

10.4 Sample Handling

Blood samples for 2 sets of tests (HbA1c and lipid profile (total cholesterol, LDL-cholesterol, HDL, triglycerides)) will be taken from all participants from both groups, at the 2 specified visits at their GP practice (baseline and 20 weeks), with an approximate maximum total volume of 9ml. All blood samples will be taken, handled, analysed and disposed of according to standard NHS procedures and local practice policy. The samples will be sent to NHS laboratories for analysis and results reported to the GP following standard procedures. Blood samples will not be stored after analysis.

10.5 Qualitative interviews in the intervention arm

We aim to assess the impact of the programme on the everyday lives of participants randomised to the eDIAMOND programme and how they report the support they had and its impact on their behaviour. Purposive sampling will be used to achieve maximum variation in demographic characteristics including age, gender, ethnicity and socioeconomic status, GP practice, and where data is available, weight loss outcomes, and any other characteristics that are found to be important during the interview and analysis process.

We will ask all participants to consent to interview at baseline, but this will be optional, and will contact to arrange interview only with those who agreed. A researcher will contact the participant by text message or telephone to arrange an interview after they have completed the 20 week intervention. Telephone interviews will be conducted lasting up to 60 minutes, covering the impact of the programme, their reactions to the behavioural support programme, and the ways that their behaviour has or has not changed, and their views of the impact of the programme. If the participant can only commit to a shorter time, we will offer alternative times to contact them in case this suits their schedule better; if they only have a shorter window of availability we will still endeavour to speak with them for the time that they do have available in order not to bias the sample against particular participant demographics e.g. working age participants who may have less availability but provide a valuable perspective on their experiences of the programme. All telephone interviews will be audio-recorded with prior participant consent.

The semi-structured interviews will follow broad topic areas based on the study objectives, but will encourage participants to discuss their opinions and experiences freely and in depth and confidentially.

Topics will include: their reported experience and impact of the intervention, how the support was experienced, and barriers and facilitators to engagement with the programme, including specific considerations of a remotely supported digitally-accessed intervention in terms of accessibility.

We anticipate that a sample of around 12 participants should hold sufficient information power to meet the defined qualitative study objectives, but will review the information power of the data throughout data collection and analysis and adapt the sample if needed.

For further details on data recording and record keeping for telephone interviews, please refer to Section 13.3

10.6 Fidelity Assessment

Intervention sessions delivered by the health coaches at Reed Wellbeing will be audio recorded on to Reed Wellbeing's call-recording system. These calls will be transferred via OneDrive to the study team who will analyse the conversations to ensure the intervention is being delivered as designed. The analysis of these sessions will also be used to guide additional training for health coaches, as and when required.

10.7 Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the trial at any time without having to give a reason.

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up – they will have the same opportunity to attend the study follow up appointment at their GP practice as participants who continue in the study. If we or the health coaches are informed that a participant has decided to stop participating in the intervention more than 2 weeks before their follow up appointment at the GP surgery is due, we will inform the GP practice of this via email in case their clinician wishes to review their medication with them (e.g., to restart medication they may have stopped – this will be at the clinician's discretion).

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. If a participant decides to withdraw from treatment, we will seek to retain them in the trial for follow-up by explaining the value to the trial of collecting follow up data from all participants by speaking with the participants. However, if the participant wishes to withdraw from follow up we will use their data up to the point that they withdraw unless they request that we do not do so. The reason for withdrawal will be recorded in the electronic case report form (eCRF).

Participants who withdraw from the trial will not be replaced. Should a participant wish to withdraw, their information held with Reed Wellbeing will be retained for 12 months following cease of use to allow the study team to analyse the performance of the programme. This relates to information provided to Reed Wellbeing by the study team and the participant. Cease of use refers to the last login to the online programme by the participant. Each participant can request that their personal information retained by Reed Wellbeing is deleted by contacting the study team, who will process that request.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Clinical decision

The type of withdrawal and reason for withdrawal, if given, will be recorded in the CRF.

10.8 Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

11. SAFETY REPORTING

We considered but decided to not record adverse events, except serious adverse events (see below section 11.1). It is hard to engage people who are in the control group (not a placebo) in recording adverse events, which seems an irrelevance to them, and these participants are also not attending appointments to collect such data. However, we will ask nurses in the intervention arm to record adverse events of special concern- namely episodes of hypoglycaemia or episodes of symptomatic hypotension that required outside assistance to manage, episodes of ketosis, or hospitalisation for international normalised ratio (INR) out of range in people on warfarin.

In addition, at 20 weeks, we will record serious adverse events for all patients, namely episodes of hospitalisation that were not planned at baseline, death or life-threatening event, illness or injury that resulted in permanent significant disability, or resulted in congenital abnormality. In the DiRECT trial, SAEs were less common in the intervention than control group. In our analysis, we will classify SAEs as diabetes-related (macrovascular or microvascular disease) or other. We will not prospectively record SAEs because this type of treatment is known to reduce the incidence of serious disease, and our retrospective recording will be sufficient to add to data on this.

11.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death

- is life-threatening (i.e., an event in which the participant 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 inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

11.2. Reporting Procedures for Serious Adverse Events

The duration of the SAE recording period for each participant lasts from their enrolment on to the study, to their completion of the study. Any serious adverse event (SAE) occurring to a participant will be recorded at the time that the research team is made aware of the incident, and reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator/clinically qualified member of the study team the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form, in accordance with HRA process.

12. STATISTICS AND ANALYSIS

12.1. Description of Statistical Methods

The primary outcome of differences in weight loss will be assessed using a generalised linear mixed model, with participant and time included as random effects and included fixed effects for duration of diabetes (≥/< 6 years) as a binary variable and trial arm. The treatment effect will be given by the treatment by time interaction, using post-estimation commands.

Secondary outcome measures for this study include other clinical outcomes: HbA1c, total cholesterol, LDL-cholesterol, HDL, triglycerides, blood pressure, and changes in diabetes and blood pressure medications. These will be analysed by analogous generalised linear mixed models with link functions appropriate for the type of data, with the same variables included and following the same procedure to assess the effect of the intervention.

We will also report process outcomes including recruitment rates and fidelity to the dietary intervention to understand whether aspects of the recruitment process and intervention could be modified.

Qualitative data from telephone interviews will be analysed thematically following a content analysis approach (11). Participant experience questionnaires will be analysed using simple summary statistics and reported descriptively.

12.2. Sample size determination

Assuming a mean weight loss of 5kg in the intervention arm and 1kg in the control arm, both with a standard deviation of 3.5 kg, we would need 21 participants per group to detect a difference of 4kg between the groups. To account for dropouts, we will recruit 30 people per group.

12.3. Decision points

The primary outcome measure for this study is weight loss. If we find significantly greater weight loss in the intervention arm compared to the control arm we will consider testing the intervention in a fully-powered trial to look at the effect on remission of T2D.

13. DATA MANAGEMENT

13.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

13.2. Access to Data

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Data will be kept in accordance with the Data Protection Act 2018. Participant identifiable information will be available to the healthcare practitioner conducting follow up as it is important that these data are known to them (they will have access to the eCRFs completed at study visits, and any records they or colleagues have made in the patients' clinical notes as is routine). Otherwise, confidentiality will be maintained and no-one outside the study team will have access to either the CRFs or the database.

13.3. Data Recording and Record Keeping

This study will be run using the Primary Care Clinical Trials Unit (CTU) standard operating procedures (SOPs) for guidance.

A study specific Data Management Plan (DMP) will be developed for the proof of concept trial outlining in detail the procedures that will be put in place to ensure that high quality data are produced for statistical analysis.

All trial data will be entered via online electronic Case Report Forms (eCRFs) into REDCap, a secure online database. The data is held on the University's secure servers and the MSD IT team provide security through Firewalls and the systems are backed up daily. Each participant will be assigned a unique study ID that will correspond to their REDCap entry.

Reed Wellbeing (Reed) will receive referrals from GP practices via NHS mail, which has inbuilt end to end encryption. These referrals will contain personal data to allow the hub coaches to contact the participant as well as containing brief medical details so that they are aware of the participant they will be speaking to. These details will be kept on their secure server, Orion. These data will be deleted within 6 months of completion of the study. Reed will complete calls using the Anyway 365 service, and will not store call recordings between participants. Data collected during call recordings will be entered into the REDCap database and will not be stored by Reed. The conversations between the Reed coach and the participant will be recorded on to their Orion system. These recordings will be transferred to the eDIAMOND study team via a OneDrive account held by the study team. On confirmation of receipt of successful transfer of the data, Reed will delete the recordings from their system.

Reed Wellbeing have been assessed by the Information Security Team by the University of Oxford and has an ISO 27001 certification.

On completion of the trial and data cleaning, the anonymised study documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held and archived for 3 years. The database will be anonymised and will be stored in a secure archiving facility. Prior to database lock, a dataset review will be undertaken by the chief investigator to ensure all queries have been resolved and the dataset is complete.

Contact details for participants will be kept separate from the research data and stored for 6 months after the end of study to allow for participants to be contacted about the results of the study.

The participant telephone interviews will be audio recorded using an encrypted, password-protected digital Dictaphone (with participants' consent). Each recording will be pseudonymised by patient ID rather than participant name. Recordings will be saved in password-protected files in a folder, with restricted access, separate from any other study data (e.g. the study database) on the University secure network. The audio recordings will be transcribed either internally or by an approved University transcriber with whom appropriate information security and confidentiality agreements are in place. File transfer (of initial audio and then transcriptions) will take place using encrypted files and a University information governance approved method for data transfer, with encryption password sent separately via different means. Transcriptions will be pseudonymised as soon as is practical, and original audio recordings deleted as soon as the transcriptions have been cross checked and the original audio is no longer required. Pseudonymised transcriptions will then be stored in a file on a secure server at the University.

Anonymised intervention group participant experience questionnaires will be completed via the RedCAP platform, which has been assessed by the University's Information Security Team and is a recommended

service for gathering confidential data due to its ISO27001 certification and additional security measures. No participant identifiable information will be collected in these questionnaires.

14. QUALITY ASSURANCE PROCEDURES

14.1 Quality Control and Quality Assurance Procedures

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. The current PC-CTU procedures will be followed for assessing risk management for trials which will outline the monitoring required. The monitoring will be carried out by the study team, who will receive appropriate training in GCP and trial procedures. Regular monitoring will be performed to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.2 Risk Assessment

A risk assessment will be conducted, and a trial specific monitoring plan developed, prior to first participant recruitment. The risk assessment will identify any trial specific risks (to both the participant's safety and well-being, and the integrity of the trial data), and the monitoring plan will detail strategies to minimise the trial specific risks identified.

Initial risk assessment has identified primary potential risks of this low-carbohydrate, low-energy approach to dietary intervention for participants:

- Risk of hypoglycaemia on oral or injectable hypoglycaemic agents. Recommendations will be made available to support GPs with stopping or adjusting oral hypoglycaemic agents on commencement and continuation of hypocaloric dieting (as would be part of routine anticipatory clinical care), such that hypoglycaemia should not occur. Likewise, patients on insulin will be excluded from eligibility for the study as the risk of hypoglycaemia would be greater in this patient group. Participants will receive guidance on how to interpret self-monitoring results from blood glucose monitoring, and when to contact their GP surgery for clinician review should unexpectedly high or low readings occur.
- It is known that sudden normalisation in retinal blood flow, associated with the return of normal glycaemic control, may result in deterioration of retinopathy (12, 13). Thus, in order for individuals to be eligible for inclusion in this study, they must have undergone diabetic retinopathy screening within the preceding 12 months. Any patient with proliferative diabetic retinopathy, or maculopathy, will be excluded, due to the potential risks of deterioration in these conditions.
- Risk of hypotension in patients taking antihypertensive medications. Recommendations will be made available to support GPs in their titration of medications according to BP readings (including home BP monitoring) – as forms part of usual clinical care for patients on antihypertensives. Participants will receive guidance on how to interpret their home monitoring BP results, and when to contact their clinician for a review should unexpectedly high or low readings occur.
- Risk of constipation. For anyone undertaking an energy-restricted diet of this nature, there is a risk that they may develop constipation. Recognising this, all participants will be warned about

the potential to develop constipation, the importance of increasing their fluid intake, how to recognise early signs of constipation, and when to contact their GP for a laxative. In the health professionals training and manual, advice on how and when to prescribe fybogel to counter constipation will be given.

- Change in INR for patients on warfarin. It is known that changes in dietary patterns can affect patients' INR values (and required warfarin dosing). Patients are routinely advised to inform their warfarin monitoring service (for example, the established RAID system in Oxford) of any significant lifestyle or medication changes, which will guide their clinicians in advising on dosing and frequency of blood tests. Patients will be advised to follow this routine advice if they are taking warfarin, and inform their monitoring service that they will be following a low-carb low-energy diet. They may then be offered an additional INR test at the clinical services' discretion.

14.3. Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Cross refer to the trial Risk Assessment and Monitoring Plan document.

15. STUDY COMMITTEES

15.1 Trial Management Group

An independent trial steering committee (PSC) will provide oversight of all matters relating to participant safety and data quality. The PSC will include at least one independent clinician, an independent statistician and a participant representative. The PSC will be asked to review the trial protocol and will provide expert advice to the Project Management Group (PMG) on the trial progress.

A data monitoring and ethics committee (DMEC) will not be convened for this study.

16. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file as per PC-CTU_SOP_TM125.

17. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1. Declaration of Helsinki

The Chief Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

18.2. Guidelines for Good Clinical Practice

The Chief Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

18.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA, and host institution for written approval.

The Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

18.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

18.5. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

18.6. Participant Confidentiality

Data will be kept in accordance with the UK General Data Protection Regulation (GDPR) and Data Protection Act (DPA)2018. The study staff will ensure that the participants' anonymity is maintained. Participant identifiable information will be available to the health care professional conducting follow up as it is important that these data are known to them. Otherwise, confidentiality will be maintained and no-one outside the study team will have access to the database. Reed Wellbeing staff will only be able to see information on the eCRF which is clinically relevant for the delivery of the intervention, for example changes in medications or blood pressure readings.

The participants will be identified only by a unique participant ID number on all study documents and any electronic databases. The personal data (i.e. contact details) will be kept in a separate, secure database from the research data. The study team will store all study data documents, including the consent form, securely. The study staff will safeguard the privacy of participants' personal data.

Any other documents holding participant identifiable information will be anonymised as soon as it is practical to do so, according to the DPA regulations. Patient identifiable data will be required for the initial screening process, and contact details in order to enable follow-up and appointments. Contact information will be deleted at the end of the trial.

18.7. Expenses and Benefits

As a result of participation in this trial, participants will be asked to attend two study visits at their local GP practice. The research team will offer each participant a £20 gift card at the 20-week follow-up visit. In addition, reasonable travel expenses to any other research-related appointments, should these be necessary, will also be reimbursed, even if the participant drop-outs of the study before it ends.

Patients will also be offered a £10 gift card to thank them for attending the online interview.

18.8. Other Ethical Considerations

There are no other noted ethical considerations.

19. FINANCE AND INSURANCE

19.1. Funding

This work is supported by the NIHR Programme Grant for Applied Research.

19.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided. NHS indemnity operates in respect of the clinical treatment that is provided.

20. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR Biomedical Research Centre, Oxford. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

21. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations.

22. ARCHIVING

On completion of the trial and once all study activity has been complete, the anonymised trial documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for three years.

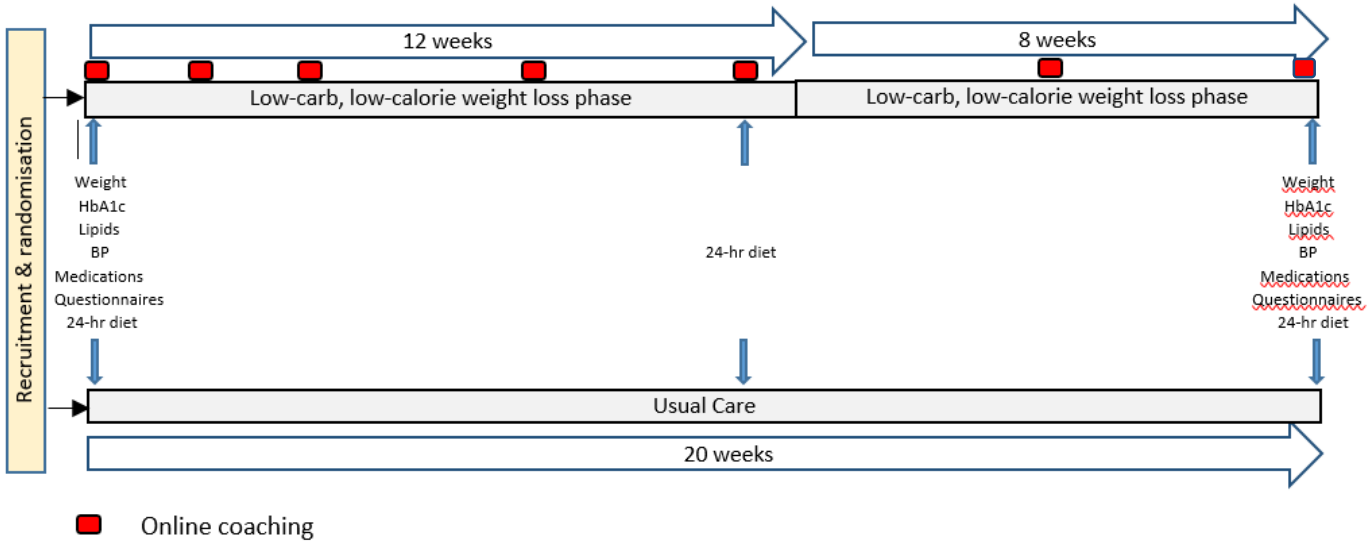
23. REFERENCES

1. DiabetesUK. Facts and Stats. Diabetes UK website, wwwdiabetesorguk. 2015.
2. Morris E, Jebb S, Aveyard P. Type 2 diabetes: treating not managing. The Lancet Diabetes & Endocrinology.
3. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet. 2018;391(10120):541-51.
4. Murdoch C, Unwin D, Cavan D, Cucuzzella M, Patel M. Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. Br J Gen Pract. 2019;69(684):360-1.
5. Unwin D, Delon C, Unwin J, Tobin S, Taylor R. What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate diet with weight loss. BMJ Nutrition, Prevention & Health. 2023:e000544.
6. Morris E, Aveyard P, Dyson P, Noreik M, Bailey C, Fox R, et al. Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND): protocol for a randomised feasibility trial. BMJ Open. 2019;9(1):e026460.

7. Morris E, Aveyard P, Dyson P, Noreik M, Bailey C, Fox R, et al. A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: A randomized controlled feasibility trial. Diabetes, Obesity and Metabolism. 2019;n/a(n/a).
8. Huntriss R, Haines M, Jones L, Mulligan D. A service evaluation exploring the effectiveness of a locally commissioned tier 3 weight management programme offering face-to-face, telephone and digital dietetic support. Clin Obes. 2021;11(3):e12444.
9. Ross JAD, Barron E, McGough B, Valabhji J, Daff K, Irwin J, et al. Uptake and impact of the English National Health Service digital diabetes prevention programme: observational study. BMJ Open Diabetes Research and Care. 2022;10(3):e002736.
10. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, et al. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. Public Health Nutr. 2011;14(11):1998-2005.
11. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15(9):1277-88.
12. Arun CS, Pandit R, Taylor R. Long-term progression of retinopathy after initiation of insulin therapy in Type 2 diabetes: an observational study. Diabetologia. 2004;47(8):1380-4.
13. Taylor R. Infortmation for Doctors. Newcastle Biomedicine Clinical Research Platforms. 2014;http://www.ncl.ac.uk/magres/research/diabetes/documents/Informationfordoctors_revised_April14.pdf.

eDIAMOND
Dietary approaches to the management of type 2 diabetes

24. APPENDIX A: SCHEMATIC OF STUDY DESIGN



25. APPENDIX B: INTERVENTION CONTENT

1. DIAMOND European Eating guide v02
2. DIAMOND support guide v04
3. DIAMOND Support guide_self monitoring instructions