Study Title: Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND) cluster randomised trial

Short title: DIAMOND

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Chief Investigator Signature: The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Professor Paul Aveyard

Conflicts of Interest Statement

Paul Aveyard has done half a day's consultancy for Weight Watchers and spoken at a symposium at the RCGP conference funded by Novo Nordisk. None of these activities led to personal payments.

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.

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Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

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1. KEY CONTACTS

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2. LAY SUMMARY

Aim

To show whether a low energy low carbohydrate food-based diet and support from practice nurses (the DIAMOND programme) can help people with recently diagnosed type 2 diabetes achieve remission, meaning no need for diabetes medicines.

Background

The DiRECT trial showed that nearly half of people with type 2 diabetes (T2D) diagnosed in the last six years had remission of diabetes following an intensive weight loss programme in which participants stopped eating their normal food and ate specially formulated "total diet replacements". However, total diet replacements do not appeal to all.

We developed the DIAMOND programme using "real food", supporting patient self-management to reduce the demand on practitioner time so it is realistic for the NHS. We tested this in a feasibility trial, which showed we could recruit people who followed the programme with nurses delivering the programme as intended. Our initial results showed 10kg weight loss and two thirds had blood glucose in the non-diabetic range at three months. We will show whether this can be maintained and how this compares to standard treatment for type 2 diabetes.

Design and methods

We will use similar processes as in the feasibility trial which recruited faster than planned. In this trial, we will recruit practices nationally, aiming to include 508 people from 56 general practices who are socially representative of the UK population. We will ask practices to write to people with diabetes who are overweight and meet the study criteria. Interested persons will be able to contact the trial team for more details. If the person appears eligible, s/he will see a nurse at the local practice who will confirm eligibility and take informed consent and then measure height, weight, blood pressure, and a blood test for blood glucose control (HbA1c) and lipid profile.

We will use minimisation based on ethnic composition and socioeconomic status to allocate practices to provide usual care for diabetes or offer the DIAMOND programme. Participants in practices offering the programme will be invited to see the nurse seven times over 6 months.

At 1 year (post-baseline visit), we will repeat the baseline measures. The main outcome is whether people have achieved remission i.e., HbA1c<48mmol/mol at 6 and 12 months and off medication. Thereafter, we will assess whether people resume treatments for diabetes and blood pressure control and the incidence of microvascular and macrovascular disease through the National Diabetes Audit.

3. SYNOPSIS

Study Title	Dietary approaches to the management of type 2 diabetes (DIAMOND) cluster randomised trial
Internal ref. no. / short title	DIAMOND
Study registration	ISRCTN 46961767
Sponsor	RGEA, University of Oxford
Funder	National Institute for Health Research – Health Technology Assessment Programme
Study Design	Cluster randomised trial
Study Participants	Adults (aged 18 to 70 years (inclusive)) with type 2 diabetes diagnosed in the past six years and with a BMI of at least 27kg/m^2
Sample Size	56 practices (approximately) recruiting 508 participants of which: 28 practices delivering the intervention (254 participants) 28 practices delivering usual care (254 participants) We will invite people to take part in interviews or discussion groups until we reach data saturation.
Planned Study Period	39 Months starting 01-April-2022 Follow up of NHS Digital data for 20 years after the end of the initial study period.
Planned Recruitment period	14-month recruitment period with a 4-month internal pilot phase May 2022 – July 2023

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To assess whether a low energy low carbohydrate diet (LELC) and behavioural support from practice nurses leads to remission in T2D patients	Remission, defined as HbA1c < 48 mmol/mol for 6 months while off diabetes medication.	Remission between 6 and 12 months assessed by medication use and measurement of HbA1c concentration at both times.
Secondary Objectives To compare effect of LELC and behavioural support from practice nurses Vs usual care on glycaemic control	Mean change in HbA1c concentration	Change between baseline and 12 months in concentration of HbA1c.
To compare effect of LELC and behavioural support from practice nurses Vs usual care on lipid profile	Change in ratio of total cholesterol/HDL	Change between baseline and 12 months in total cholesterol/HDL ratio
To compare effect of LELC and behavioural support from practice nurses Vs usual care on blood pressure	Change in systolic and diastolic blood pressure	Change in systolic and diastolic blood pressure between baseline and 12 months
To compare effect of LELC and behavioural support from practice nurses Vs usual care on cardiovascular risk	Change in QRISK2 score or SMART score	Change in QRISK2/SMART score between baseline and 12 months
To compare effect of LELC and behavioural support from practice nurses Vs usual care on quality of life	Change in Problem areas in diabetes (PAID) score and WHO-5 measure of wellbeing	Change between baseline and 12 months in PAID and WHO-5 scores.

Process measures To compare effect of LELC and behavioural support from practice nurses Vs usual care on diet quality	Change in consumption of total carbohydrate, fibre, and free sugars	Change in food intake recorded in Intake24 questionnaire between baseline and 12 months in total carbohydrate, fibre, free sugars consumption
To compare effect of LELC and behavioural support from practice nurses Vs usual care on weight	Change in weight	Change in weight between baseline and 12 months
To assess the impact of the programme on participants' lives and behaviour	Qualitative analysis and questionnaire	Analysis of interviews at various stages of the programme; questionnaire at 6 months
Exploratory outcome To compare effect of LELC and behavioural support from practice nurses Vs usual care on risk of liver fibrosis	Change in FIB-4	Change in FIB-4 between baseline and 6 and 12 months
To assess the feasibility of recruitment via text and letter	Proportion of practices with capacity to recruit by both text and letter; proportion of practices randomised to text vs to letter that proceed to aid recruitment by additional means (subsequent texts, letters, or telephone calls)	Practices recruiting by text and letter and aiding recruitment by additional means throughout the recruitment period.
To compare recruitment using text messages Vs Docmail mail out	Difference in number of patients recruited; rate at which they are recruited; and demographics of participants recruited, between text and docmail	Patients recruited in practices using text messages and patients recruited in practices using Docmail mail out throughout the recruitment period
Intervention(s)	A low-energy, low-carbohydrate food-base diet providing 800 – 1000 kcal/ day with behavioural support from a practice nurse (the DIAMOND programme)	
Comparator	Usual Care	

4. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form

GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
LELC	Low Energy Low Carbohydrate
NHS	National Health Service
OR	Odds ratio
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RES	Research Ethics Service
RGEA	Research Governance, Ethics & Assurance, University of Oxford
RR	Risk ratio
SOP	Standard Operating Procedure
T2D	Type 2 Diabetes
TDR	Total Diet Replacement
VLCD	Very Low Calorie Diet

5. BACKGROUND AND RATIONALE

The Diabetes UK priority setting partnership for type 2 diabetes (T2D) involved hundreds of people living with diabetes and suggested that the following questions were in the top ten priorities:

- Can T2D be cured or reversed, what is the best way to achieve this and is there a point beyond which the condition can't be reversed?
- How can people with T2D be supported to make lifestyle changes to help them manage their condition, how effective are they, and what stops them from working?
- Should diet and exercise be used as an alternative to medications for managing T2D, or alongside them?
- What role do fats, carbohydrates and proteins play in managing T2D, and are there risks and benefits to using particular approaches?

In this protocol we describe a trial to examine the effectiveness of an intervention to put T2D into remission that addresses each of these priorities. It builds on a behavioural programme we developed that aims to support patients to change their diet, to lose weight and improve their blood glucose control, particularly by altering their carbohydrate intake.

International guidelines suggest that an optimum diet for diabetes is one that promotes energy balance with around 45% of energy coming from carbohydrates, ideally low glycaemic index carbohydrates[1]. However, there is significant controversy about the most appropriate amount of carbohydrate, which we address below.

Aside from diet composition, weight loss is also key. NICE guidance is that people who are classed as overweight should be advised to lose 5-10% of body weight. Currently, T2D is mostly diagnosed and managed initially in primary care, but support for weight loss is the exception not the norm. One study reported that 46% of people with T2D had received weight loss advice[2]. However, we know that offering support improves weight loss over offering basic advice to lose weight[3]. Currently, 73% of people with newly diagnosed T2D were offered and only 12% were recorded as attending diabetes structured education[4]. This education provides dietary advice, but not support to lose weight. For people with obesity in general, GP intervention to support weight loss is unusual, with the most recent estimates suggesting around 5% of people per year receive advice and around 3% referral for weight loss support[5], despite the obesity indicator in the Quality and Outcomes Framework. People with T2D were 83% (75 to 92%) more likely to receive advice or support, but this suggests only around 5% of people with T2D get offered active support to lose weight. Thus, the current system offers rather patchy support to lose weight or for the dietary management of diabetes.

Weight loss can induce remission of type 2 diabetes

We searched Medline with terms for 'weight loss', 'type 2 diabetes', and 'remission'. We found a systematic review and meta-analysis of 621 cohort studies of bariatric surgery with an average of 55% total body weight loss resolved T2D in 78%. Greater weight loss was associated with greater remission[6]. A 2018 review included seven randomised controlled trials (RCTs) with an average follow-up of 2 years. Compared with medical management, T2D remission was observed in 138 of 263 patients (52.5%) with bariatric surgery compared to seven of 200 patients (3.5%) (risk ratio (RR) 10, (95% confidence interval 5.5 to 17.9). A further review, including mainly cohort studies, showed that bariatric surgery compared with standard management was associated with lower microvascular (RR 0.37 (0.30 to 0.46) and macrovascular events (RR 0.52 (0.44 to 0.61), and mortality (RR 0.21 (0.20 to 0.21) compared with standard diabetes care[7].

Substantial weight loss can be achieved without surgery

We searched Medline for systematic reviews using terms very low energy diet (providing less than 800 kcal/day), low energy diets (<1200kcal/day), and weight loss. One systematic review included 12 trials of very low energy diets published before November 2014[8]. Ten trials compared a behavioural support programme plus a very low calorie diet (VLCD) to a behavioural support programme delivered by a multidisciplinary clinic (equivalent to tier 3 weight loss programme). Mean weight loss at one year was 6.4kg in the behavioural support programme, with people assigned to VLCD losing 10.3kg, an additional 3.9kg (-6.7 to -1.1). At follow-ups to five years, there was greater weight loss in the VLCD group, but data were sparse. Glycaemic control and blood pressure were somewhat lower in the VLCD arms, but there was imprecision. A subsequent systematic review that included low energy total diet replacement programmes as well as very low energy programmes showed that weight loss achieved by people with T2D was similar to people without diabetes.[9]

The trials described above all took place in specialist obesity clinics, and it was thought that total diet replacement (TDR) programmes requiring participants to give up all food were unlikely to be acceptable, effective, or safely delivered in primary care. Since these reviews, two randomised trials have published,

showing that these programmes deliver comparable outcomes when delivered by non-specialists in primary care as when delivered by specialists in multidisciplinary obesity clinics. Our trial, DROPLET, offered TDR for eight weeks, with partial replacement for four more weeks with support compared with weight loss support from practice nurses. The TDR led to 15.1kg weight loss at 6 months and 10.7kg weight loss at 12 months, a difference of -7.2 kg (-9.4 to -4.9 kg) over weight loss support from a practice nurse[10]. The DiRECT trial randomised participants with new onset T2D to either TDR with support or usual care (no weight loss intervention).[11] Weight loss at 12 months was 10.0 kg in the intervention group and 1·0 kg in the control group (adjusted difference -8.8kg (-10.3 to -7.3). In both trials, the programmes were delivered with evidence of safety, adverse effects were mild, and quality of life improved in the intervention groups compared with control, and the majority of people assigned to TDR persisted with the programme. Contrary to expectations, low energy diets can be offered in primary care and lead to substantial weight loss. The DiRECT trial showed that 46% of people randomised to the intervention went into remission of T2D at one year compared with 4% in the control group, (odds ratio (OR) 19·7 (7·8 to 49·8), and at two years the corresponding figures were 36% and 3%, OR 25·8 (8·3 to 80·8)[12]. The probability of remission was linearly associated with weight lost, and weight loss was the only meaningful predictor of remission[13].

TDR programmes are not the only way to achieve substantial weight loss. We have recently conducted a feasibility trial of the intervention we propose testing here (DIAMOND). We emulated the low energy diet approach, because the systematic review above showed that the weight loss relative to control was proportional to the difference in energy prescription.[9] We therefore devised a weight loss programme delivering about 800-1000kcal/day with participants eating everyday food. We followed the person-based approach to intervention development, with iterative cycles of patient and practitioner involvement to refine the intervention (described below).[14] Nurses delivered low intensity behavioural support and participants had extensive support materials. The trial took place in three general practices and recruited 33 participants ahead of schedule. Participants in the control group were randomised to usual care. It passed all its feasibility criteria comfortably, namely recruitment, acceptance of the intervention, adherence by nurses, and follow-up[15].

Nurses supported participants to lose weight over eight weeks while following the programme, with weight loss maintenance for the next four weeks. Mean (SD) weight loss in the intervention group was 9.5 kg (5.4 kg) compared with 2.0 kg (2.5 kg) in the control group (adjusted difference − 7.5 kg [−11.0 to −4.0, P < 0.001])[15]. Mean reduction in HbA1c in the intervention group was 16.3 mmol/mol (13.3 mmol/mol) compared with 0.7 mmol/mol (4.5 mmol/mol) in the control group (difference −15.7 mmol/mol [−24.1 to −7.3, P< 0.001]). Systolic blood pressure was lower: −9.6mmHg (16.2) versus 4.8 (10.6), adjusted difference −14.4 (−25.8 to −3.0), P=0.010, and diastolic −5.3 (11.0) versus 0.5 (8.8), adjusted difference −6.0 (−13.7 to 1.8), P=0.130. While these estimates of clinical effect are imprecise, they offer promising evidence of potential long-term effectiveness. Based on the participant feedback, in the trial proposed below, we plan to extend the weight loss period for 12 weeks, or longer if the participant and the nurse feel this is appropriate, before transition to the maintenance programme.

In this feasibility trial, we looked for evidence of contamination and found it[15] The weight loss in the control group was driven by three participants following some version of the intervention, prompted by the enrolment process and the need to visit, for the nurse to discuss their diabetes and their weight and receive advice, with follow up 3 months later. Moreover, nurses reported feeling uncomfortable withholding the intervention from control participants. We therefore propose to enrol practices and

patients through the Clinical Research Network (CRN) and then randomise practices to usual care or the DIAMOND programme to reduce the possibility of contamination.

We believe there is room for the DIAMOND programme alongside other weight loss interventions for people with T2D to manage their condition or put it into remission. First, the national rollout of the TDR programme in England is confined to people who have been diagnosed for less than six years. NHS England estimate that this is about a tenth of the population with T2D. In DIAMOND, we enrolled anyone with T2D regardless of duration. Whilst we saw preliminary evidence that reduction in HbA1c was related to duration of diabetes, there was no such evidence nor reason to suspect that blood pressure reduction would be affected by duration of diabetes. Second, DIAMOND is likely to cost less than £100 to deliver compared with around £1400 for TDR, making it a realistic treatment option beyond the drive to achieve remission. Third, it is unlikely that a programme that asks people to consume only food replacement products for 12 weeks will achieve universal take-up by those who might benefit. DIAMOND, which uses usual food, would allow a shared meal experience with household members that TDRs may not. In DiRECT, 28% of people offered TDR agreed to enrol and of them, 72% were suitable, meaning only 20% overall participated. While the context of the trial and the uncertainty of benefit may have put-off some, it remains unlikely that everyone who wants to lose weight will want to do so with TDR. Our PPI group certainly agreed that they would prefer a weight loss programme using usual food, not formula products. They were concerned about the social acceptability, the palatability of products, and it did not fit with their internal model of a sustainable weight management intervention.

Weight regain is slow and does not remove the benefit of weight loss interventions.
One concern about weight loss interventions, particularly those that induce rapid weight loss through replacing all normal food, is that they will be followed by rapid weight regain. We searched for and found only one experimental study that directly addressed the question of whether a slower and “more sustainable” food-based weight-reduction led to less or slower weight regain that total diet replacement by randomising participants to one or the other approach to weight loss, both with behavioural support. The study reported greater success for the rapid weight loss (TDR group) - a higher proportion of people reached the target 10% weight loss, but thereafter, weight regain occurred at the same rate, regardless of whether it had been achieved with a TDR or with a “more sustainable food-based approach”. In our review of 249 weight loss trials described below, greater weight loss was associated with faster regain, but it took at least five years for the greater initial weight loss to be removed by regain[16].

We have just completed the largest systematic review to date of behavioural weight loss programmes examining the rate of weight regain following the end of programmes[17]. We synthesised data from 249 trials with longest follow-up of 30 years. Estimates based suggest that weight regain after programmes cease occurs faster in groups given support to lose weight (and therefore who achieve greater weight loss) than in control groups, at a rate of approximately 0.01 to 0.03 kg/month (0.12kg to 0.32kg/year), with a difference between intervention and control maintained for at least five years, after which data were sparse. The incidence of diabetes, hypertension, and cardiovascular disease was lower for people in the intervention groups. Behavioural weight management programmes also reduced blood pressure, improved lipids, and improved glycaemic control relative to minimal intervention. The difference in incidence of disease and risk factors between weight management programmes and minimal intervention narrowed over many years, with evidence that slower weight regain (relative to control) meant benefits lasted longer. Given the evidence that temporary reduction of lipids leads to permanent reduction in incidence of cardiovascular disease,[18] these data suggest that weight regain does not abolish the benefits

of weight loss programmes. Weight management programmes should reduce the incidence of cardiovascular and diabetes-specific complications in people with type 2 diabetes. This is supported by a systematic review of 54 RCTs of weight-loss interventions with 30,206 participants which found that weight loss interventions decrease all-cause mortality (risk ratio 0.82, (0.71 to 0.95))[19].

Low carbohydrate diets may be particularly helpful in T2D

We designed the DIAMOND programme primarily to be low energy, but we focused on reducing energy from carbohydrate foods specifically for several reasons. First, there is a good deal of public demand to follow low carbohydrate programmes and our PPI group and the Diabetes UK priority setting group reflects this. Second, there is evidence that weight loss programmes that include clear rules for diet achieve better weight loss[20], and omitting all major carbohydrate sources is a clear rule. Third, there is evidence that there may be specific benefits of low carbohydrate diets (LCDs) in people with type 2 diabetes by reducing post-prandial glucose excursions,[21] and reducing liver and pancreatic fat, as measured with magnetic resonance imaging,[22] which may restore insulin sensitivity and secretion, even in the absence of weight loss[23] We drew on the draft Scientific Advisory Committee on Nutrition (SACN) review of reviews of the effects of low carbohydrate diets in type 2 diabetes[24]. Twelve systematic reviews have reported that LCDs improve glycaemic control and weight loss short-term, but with no evidence of a difference in weight by 6 months or in HbA1c at one year and longer, probably due to declining dietary adherence[25-36] Despite this, LCDs are currently increasingly being recommended and followed in practice. SACN concluded that further studies of the long-term effects of low-carbohydrate diets in T2D were needed. There are no such trials registered and this proposal aims to fill the gap.

Dietary fibre reduces cardiovascular risk

SACN also expressed concerns about longer-term health associated with low carbohydrate diets since there is good evidence that consuming carbohydrate-containing foods that provide significant amounts of dietary fibre is associated with reduced cardiovascular risk. A 2019 systematic review of 58 RCTs showed that allocation to higher fibre carbohydrates compared with usual diet reduced bodyweight, systolic blood pressure, and total cholesterol[37]. The same systematic review included 185 cohort studies found a 15-30% decreased incidence of cardiovascular disease, all-cause mortality, and incidence of type 2 diabetes with higher fibre diets.

The importance of carbohydrate quality, especially for people with T2D, is emphasised by the Diogenes trial. Following weight loss with a TDR programme, people receiving advice to follow a high protein, low glycaemic index (GI) diet gained less weight than a 'usual diet' or lower protein, higher GI diet[38]. Re-analysis showed that those with elevated baseline fasting glucose obtained a particular advantage, gaining far less weight on the low GI diet than allocation to higher GI diet[39] This was replicated in re-analysis of two other trials where the intervention was a low glycaemic diet[39] Together, the data suggest it is possible and perhaps preferable for people with type 2 diabetes to consume modest amounts of carbohydrate that is low GI, fibre-rich and we have incorporated this evidence into the maintenance programme in this trial.

The role of weight loss programmes in supporting improvement in non-alcoholic fatty liver disease (NAFLD)

About 20% of people with type 2 diabetes and obesity have advanced liver fibrosis due to non-alcoholic fatty liver disease which progresses slowly and is an independent risk factor for morbidity and mortality. Fibrosis is typically undiagnosed until it progresses to cirrhosis with complications and currently the identification of patients with fibrosis remains challenging.

Risk stratification scores, such as the blood-based FIB-4, have been proposed as non-invasive tests to refer patients suspected of advanced liver fibrosis (in the presence of a negative liver screen) from primary to specialist hepatology care. These are combinations of 'routine' blood tests that can be performed inexpensively and are commonly performed as part of routine health monitoring in primary care.

Given the lack of effective pharmacological treatments, current hepatology care for people with NAFLD and fibrosis includes monitoring disease progression, enrolling patients in clinical trials, and advising substantial weight loss, the only effective treatment for regressing liver fibrosis. The achievement of substantial weight loss (and fibrosis regression) minimises the need for frequent monitoring of disease progression. Given this, identification and initial management through providing weight loss support could be effectively implemented in primary care among people at high risk for advanced fibrosis. This would require evidence that risk stratification tests are responsive to weight loss to an extent whereby patients can move from a "high-risk" (for fibrosis) to a "low-risk" category. A recent study provided promising evidence that this might be the case as it suggested that weight loss is also associated with reductions in the risk stratification tests FIB-4 in a dose-response manner among patients with biopsy-proven fibrosis.[40] Here we propose a substudy to assess the effect of the DIAMOND intervention on risk of fibrosis as measured by FIB-4. This poses no additional burdens on participants and requires no additional costs for the research other than research time from an external member of the research team.

Long term follow up through National Diabetes Audit

The NHS collects information about patients with diabetes and their care as part of the National Diabetes Audit. This is an NHS programme to improve the quality of care that the NHS gives to people with diabetes. We will use participants' NHS number to collect information about their health through the National Diabetes Audit. We will ask participants to agree to flagging of their records by NHS Digital and will extract data from the National Diabetes Audit on weight, HbA1c, blood pressure, lipids, and the occurrence of macrovascular and microvascular disease.

Study within a project (SWAP) on recruitment methods

We propose a Study Within A Project (SWAP) within the DIAMOND cluster randomised trial, to evaluate whether participant recruitment by text is feasible, is acceptable to primary care practice sites, and affects the speed of recruitment or demographics of patients recruited compared with recruitment by postal letter.

The most commonly used strategy for recruitment to trials in primary care is using letters sent through the post (often via an intermediary company such as Docmail), where sites (here, GP surgeries) send invitation letters, often with additional printed information such as participant information sheets (PIS), via Royal Mail; participants may reply by returning a reply slip via post or contact the study team through other means. In a large, multi-site trial such as DIAMOND, with a recruitment target of over 500 participants, and a predicted recruitment rate of 10% from invitation letters, up to 5000 letters may need to be sent for recruitment alone. Between posting and printing, this alone would generate 0.1-0.2 tonnes of CO_2 emissions – the equivalent of flying by plane from London to Paris 5 times. With the carbon emissions for an average text estimated to be 0.014g CO_2 , compared to around 30-40g per letter (and 4-20g per email) this represents an opportunity for a significant reduction in carbon emissions were a large trial to switch to text messages for the primary recruitment strategy [41].

Use of text messaging services in primary care have increased significantly since the COVID-19 pandemic[42]. However, given wider concern that use of digital and mobile technologies may widen existing health inequalities and may fail to reach traditionally underserved populations – a concern that was also highlighted by our patient and public involvement panel - any proposed change in recruitment strategy requires careful evaluation of the impact on both practices and participants.

To our knowledge there are no studies systematically evaluating recruitment to a study within primary care using text and letter methods. Here, we aim to evaluate:

1. The feasibility of recruitment via text and letter
    a. What proportion of practices have capacity to recruit by both text and letter
    b. What proportion of practices randomised to text vs to letter proceed to aid recruitment by additional means (subsequent texts, letters, or telephone calls)
2. The impact on recruitment rates for participant invitations sent via text vs letter
    a. Number of participants recruited by text vs by letter
    b. Proportion of responses to invitation by text vs by letter
    c. Speed of recruitment (contact in <24hours, <72 hours, <1 weeks, >1 week)
3. The impact on the demographics of patients recruited by text vs by letter
    a. Age, gender, ethnicity, socioeconomic status

The main expected benefits of this SWAP are twofold:

1) To identify whether recruitment by text message, which markedly reduces carbon emission compared to traditional methods, is feasible for future studies.
2) To contribute to the methodological literature by evaluating recruitment processes via text and letter for studies in primary care, quantifying any difference in recruitment and response rates, and any impact on recruited participant demographics. We will disseminate findings to the NIHR UK Regional Research Delivery Networks (RRDNs) and research active practices, including via presentation at the regional research in practice symposium.

6. OBJECTIVES AND OUTCOME MEASURES

The aim is to assess whether a low energy, low carbohydrate diet (providing 800-1000kcal/ day) and behavioural support from practice nurses is more likely to lead to remission compared with usual care in adults with T2D diagnosed in the last six years. The objectives are to assess the impact on:

- diabetes remission
- glycaemic control
- cardiovascular risk
- weight

- wellbeing and diabetes distress
- diet quality
- cost-effectiveness over the lifetime and return on investment in the short-term. This will be assessed outside the trial through modelling and these outcomes do not appear in the table below.
- Change in FIB-4 score

We will also assess equity of programme uptake and in exploratory subgroup analyses, we will assess the impact of the programme by age, gender, socioeconomic status, ethnicity, duration of diabetes, and number of medications for diabetes used at baseline.

We will assess these same outcomes over the longer-term through linkage through NHS Digital/ National Diabetes Audit. We will assess the impact of recruitment method.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To assess whether a low energy low carbohydrate diet (LELC) and behavioural support from practice nurses leads to remission in T2D patients	Remission, defined as HbA1c < 48 mmol/mol for 6 months while off diabetes medication.	Remission between 6 and 12 months assessed by medication use and measurement of HbA1c concentration at both times.
Secondary Objectives To compare effect of LELC and behavioural support from practice nurses Vs usual care on glycaemic control	Mean change in HbA1c concentration	Change between baseline and 12 months in concentration of HbA1c.
To compare effect of LELC and behavioural support from practice nurses Vs usual care on lipid profile	Change in ratio of total cholesterol/HDL	Change between baseline and 12 months in total cholesterol/HDL ratio
To compare effect of LELC and behavioural support from practice nurses Vs usual care on blood pressure	Change in systolic and diastolic blood pressure	Change in systolic and diastolic blood pressure between baseline and 12 months
To compare effect of LELC and behavioural support from practice nurses Vs usual care on cardiovascular risk	Change in QRISK2 score or SMART score	Change in QRISK2/SMART score between baseline and 12 months
To compare effect of LELC and behavioural support from practice nurses Vs usual care on quality of life	Problem areas in diabetes (PAID) score WHO-5 measure of wellbeing	Change between baseline and 12 months in PAID and WHO-5 scored.
Process measures To compare effect of LELC and behavioural support from practice nurses Vs usual care on diet quality	Change in consumption of total carbohydrate, fibre, and free sugars	Change in Intake24 between baseline and 12 months in total carbohydrate, fibre, free sugars consumption
To compare effect of LELC and behavioural support from practice nurses Vs usual care on weight	Change in weight	Change in weight between baseline and 12 months
To assess the impact of the programme on participants' lives and behaviour	Qualitative analysis and questionnaire	Analysis of interviews at various stages of the programme; questionnaire at 6 months

Exploratory outcome To compare effect of LELC and behavioural support from practice nurses Vs usual care on risk of liver fibrosis	Change in FIB-4	Change in FIB-4 between baseline and 6 and 12 months
To assess the feasibility of recruitment via text and letter	Proportion of practices with capacity to recruit by both text and letter; proportion of practices randomised to text vs to letter that proceed to aid recruitment by additional means (subsequent texts, letters, or telephone calls)	Practices recruiting by text and letter and aiding recruitment by additional means throughout the recruitment period.
To compare recruitment using text messages Vs Docmail mail out	Difference in number of patients recruited; rate at which they are recruited; and demographics of participants recruited, between text and docmail	Patients recruited in practices using text messages and patients recruited in practices using Docmail mail out throughout the recruitment period
To assess long term benefits of the programme through National Diabetes Audit	Weight, HbA1c, blood pressure, lipids, and the occurrence of macrovascular and microvascular disease	20 years beyond the end of the initial study period

7. STUDY DESIGN

The study will be a pragmatic cluster randomised trial whereby approximately 56 practices will be randomised to either deliver the DIAMOND Programme or usual care.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

We are seeking to enrol 508 people diagnosed with T2D in the last 6 years from approximately 56 practices.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study
- Adults (aged 18 to 70 years (inclusive)) with type 2 diabetes diagnosed in the past six years
- A BMI of at least 27kg/m^2 and who may benefit from achieving remission

- Able to attend baseline visits, adhere to intervention and follow-up appointments
- Participant is registered at a GP practice that is open and randomised

8.3. Exclusion Criteria

- Currently diagnosed with type 2 diabetes but who are in remission using the NHS diabetes remission criteria
- Currently using insulin injections
- GLP1-agonists or SGLT2 inhibitors started in the 3 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 or planning to breast feed
- Diagnosed with a recent myocardial infarction or stroke in the past three months, uncontrolled cardiac conduction abnormalities e.g. long QT syndrome, 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), other current severe illness or 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 DIAMOND or the other research study/ies that they are participating in.

There will be no exceptions made to allow into the study people who do not fulfil all these criteria.

9. PROTOCOL PROCEDURES

9.1. Screening and Eligibility Assessment

Enrolling general practices

We are seeking a nationally representative set of practices, so we will use quota sampling to facilitate this. We will create a quota of practices that represent England based on deprivation based on the following index of multiple deprivation (IMD) decile groups- 1-4, 5-7, 8-10, and ethnicity as percentage non-white in increments (0-8.9, ≥9.0). Nine percent of the English population in the relevant age group (40-64 years) is from a non-white ethnic group. We will create a database of practices holding details expressing interest that holds the practice details, population size, IMD decile, and ethnic composition. This database will cover the progress of the practice through the recruitment process from expression of interest to green light. Practices will fill slots in the quota and as practices formally enrol, we will cease accepting expressions of interest from practices that will worsen any imbalance and accept those from practices that facilitate our nationally representative recruitment.

Enrolling patients within practices

We aim to enrol adults with T2D diagnosed in the past six years and with a BMI of at least 27kg/m^2 and who may benefit from achieving remission. These criteria match those of DiRECT and the NHS T2D remission programme. They also match NHS England TDR rollout.

Practices will search their registers for potential participants. Practices will invite patients by letter and interested patients will contact the trial team, be screened for eligibility, and booked for an appointment with the person facilitating recruitment (CRN nurse or equivalent). In addition, we will financially support practices to call selected patients to ensure representation from typically under-represented groups. We have previously found that recruitment by letter alone tends to lead to a somewhat higher uptake by more affluent people[43], while in-person offer leads to higher take-up by the more deprived[44]. The CRN nurse (or equivalent) will see all potential participants to confirm eligibility and consent them onto the trial.

We will develop a search strategy for each computer system that enables us to define a cohort to invite into the study based on coded medical records. GPs will be asked to screen this list to remove patients for whom the invite would be inappropriate and where this is not easily coded, for example people who have been recently bereaved or known to be violent. GPs will invite by letter (including via Docmail) or text message patients who appear eligible and suitable. In addition, because this procedure tends to over-recruit more affluent patients and women, we will ask practices to phone and invite participants who do not respond to the initial letter or text message and invite them to consider the study. The letter, text message and the phone call will ask participants to contact the trial team for further information.

The trial team will outline the nature of the study and its requirements and respond to patients' questions, when they initially express interest in taking part. If the patient is interested to participate, the trial team will check eligibility using a checklist of inclusion/exclusion criteria where these are appropriate for use by a non-clinician. For people who are interested to join the study, the trial team will send the PIS and book an appointment for a baseline visit. We aim to have a relatively equal cluster size and so will book a quota of baseline visits and place later participants on a waiting list, inviting them to a baseline visit if insufficient participants are enrolled.

CRN nurses (or equivalent) will perform baseline visits where participants will be consented, and eligibility will be confirmed. Once eligibility is confirmed participants will be enrolled onto the trial. Participants enrolled at GP practices randomised to deliver usual care will be provided with details by the GP practice. Participants enrolled at GP practices randomised to deliver the DIAMOND programme will see practice nurses (or equivalent suitably qualified practice staff). Nurses offering the DIAMOND programme will provide two hours of support over seven appointments over six months plus comprehensive resources, co-developed by people with diabetes. We will provide online nurse training, a pragmatic model for the NHS with access to an online webinar to allow nurses and doctors to ask questions.

NIHR Carbon Reduction and Sustainability: sustainability delivery of research- Pilot

Participating practices will be recruiting patients to join the study using either Docmail paper mail out or text messages, supported with phone calls where appropriate, as outlined above. Studies within primary care typically recruit using paper mail outs, such as Docmail. However, text messaging services to patients from their GP practice are becoming an increasingly common method of communication and offers an opportunity to recruit patients to research in a more environmentally sustainable approach than

traditional paper mail outs. However, we do not know if this is a feasible approach to recruit patients to research in primary care and we are aiming to evaluate if using text messages can be suitably used to recruit patients.

We will offer participating GP practices the opportunity to opt into this evaluation. Practices who opt in will be randomly allocated to recruit by either text message or Docmail paper mail out. If the recruitment method that they are allocated to is unsuccessful, we will support them to supplement recruitment using the recruitment method that they were not initially allocated to and/or telephone calls. It is not mandatory for practices to take part in this sustainability pilot and they can opt out if they do not have infrastructure in place to support one of the two methods of recruitment. We will ask all practices participating in the study to report on the demographic and socioeconomic characteristics of patients eligible to be invited to take part. We will collect anonymised data from patients who express an interest in taking part to evaluate whether the different recruitment methods preferentially recruit different populations.

9.2. Informed Consent

Written versions of the participant information and informed consent form will be presented to the participants detailing 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 current or future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant information sheet will be sent to participants who respond to the trial team and express interest, pass initial eligibility checks, and book a baseline appointment. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the investigator, their GP, the CRN nurse, or other independent parties to decide whether they will participate in the study.

Evidence of informed consent will then be obtained by means of participant-dated signature and dated signature of the person who undertook the baseline visit. The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief Investigator. A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the Trial Master File and a copy will be filed at the study site and included in the medical notes.

9.3. Randomisation

In this pragmatic two-arm parallel groups cluster randomised trial, we will allocate general practices to deliver either the DIAMOND programme or usual care using minimisation based on deprivation and ethnicity. It is possible that these factors may influence the success of the approach. For example, low carbohydrate diets are perceived as expensive, because staple carbohydrate foods have a low cost/calorie and, in some cultures, carbohydrate-containing foods represent a much larger proportion of total energy than the population average and may be harder to restrict. Practices will be allocated after participants

have been booked for the initial visit to prevent selection bias. We have chosen cluster randomisation because nurses who had been trained found not supporting participants in the control group difficult in our feasibility trial and because of evident contamination.

We will create three strata to define IMD and two to define ethnicity. The strata for deprivation are based on IMD score (1-4, 5-7, 8-10) and halves of the % non-white British (0-8.9, ≥9.0). Using Sortition, we will create a minimisation programme that balances these characteristics but incorporates a random element. The trial team will enrol practices once we have reached a quota of 8 participants booked for an initial visit. Allocation will be concealed using Sortition.

9.4. Blinding and code-breaking

This is an open-label study in which participants, clinicians, and trial staff will know the allocation of the practice. We consider the risk of bias to be low, as the outcomes are measured objectively. Once a practice has been allocated to intervention or control, the CTU will inform the practice of this, and they will proceed with staff training or continue usual care as appropriate. The trial statistician(s) will remain blinded to treatment allocation when performing the final analysis.

9.5. Description of study intervention(s), comparators and study procedures (clinical)

9.5.1. DIAMOND Programme

Patients will be advised that with full adherence, the diet is designed to achieve 15kg weight loss. Nurses or suitably qualified alternatives will support patients to achieve this target wherever possible since our weight regain review shows strongly that greater initial weight loss is predictive of greater long term health benefits. The nurse will discuss the participant's goals for their diabetes and health and how remission may achieve these goals. They will see participants at 0, 2, 4, 8, 12, 16 and 26 weeks from the start of the programme, but respond flexibly to participants' needs, as would be the case in routine care. Appointments are up to 20 minutes long in up to week 12 and 10 minutes thereafter. We expect these to be face-to-face, but remote consultations may be appropriate in some circumstances.

The DIAMOND programme is a behaviourally informed low-energy, low-carbohydrate diet delivered by practice nurses in primary care. It draws on the motivational value of the relationship between the practice nurse and the patient for delivery and to provide behavioural support, but it provides most technical knowledge through structured materials such as meal plans, addressing professionals' uncertainties[14].

The dietary component of the DIAMOND programme is a low-energy low-carbohydrate diet (800-1000kcal with a maximum of 50g carbohydrate per day, or 20-25% total energy, compared to usual intake of 45%). The core principles include advice to exclude all sugary and starchy foods except very limited dairy and fruit, strict portion control and avoiding energy-dense foods. The maintenance programme supports a transition to a sustainable dietary regimen to control energy intake, provide about 125g/d carbohydrate, less than half the average population intake (for example, 200 ml milk, 2 portions fruit and a modest portion of fibre-rich carbohydrate at each of three meals). It is based around the 3Rs: refrain (from high sugar foods e.g. cakes and biscuits), restrict (frequency and portions of starchy carbohydrates), and replace (swap to high fibre varieties of carbohydrate).

We will provide online nurse training, a pragmatic model for the NHS with access to an online webinar to allow nurses and doctors to ask questions. The design of these training modules, based on those tested in the DIAMOND feasibility study, was informed by behavioural analysis of the existing qualitative literature and findings from the feasibility study, identifying critical domains of the Behaviour Change Wheel and Theoretical Domains Framework[45, 46], to promote successful behaviour change in the healthcare professional delivering the intervention and facilitate effective delivery of the programme. Using these frameworks, key influencing factors which the training targets are: psychological capability (including knowledge and skills – explaining the scientific rationale for this approach, evidence of effectiveness in other studies/settings, basic dietary principles, and training in brief motivational and behaviour change techniques for consultations), social and physical opportunity (structured dedicated intervention sessions with time set aside to deliver, to facilitate comprehensive but efficient delivery), and reflective motivation (sharing case experiences of healthcare professionals involved in the feasibility study who described how seeing the changes in their own patients improved their own motivation to engage, and the changes they could expect to see). Process analysis of the feasibility study also highlighted the positive impact of providing simple checklists for each intervention session, to ensure core concepts and actions were covered, and the structured comprehensive patient materials designed to contain most core knowledge required for the programme, which could be used independently by patients but also for signposting during the healthcare professional's consultations, serving as effective prompts and giving the healthcare professional confidence that they needed little to no specialist dietary knowledge to support the patient in undertaking the intervention.

We will ask clinicians to withdraw medication for hypertension and diabetes following the protocols used for the NHS Diabetes Remission Programme i.e. on starting the DIAMOND programme and also to ask patients to inform their local warfarin monitoring service, who may advise an additional blood test. Participants will be advised to measure and record their BP and fasting blood glucose two days per week, which reinforces adherence and reassures participants and clinicians. We will advise participants to contact their GP using a traffic-light system based on guidance in the national rollout of the diabetes remission programme.

9.5.2. Usual Care Arm

Consistent with the pragmatic trial design, we aim to compare the DIAMOND intervention to current usual care for people with diabetes. While 'usual care' risks some diversity in practice, the alternative would be to create a bespoke package for the control group which would in itself constitute a new intervention. "Usual care" includes referral to diabetes structured education with the primary goal to control blood glucose levels and to reduce long term cardiovascular risk. It does not include specific support for weight loss, though people with type 2 diabetes are encouraged to achieve and maintain a healthy weight and to adhere to population diet and physical activity guidance.

9.6. Baseline Assessments

At baseline, the CRN nurse (or equivalent) will use the medical records and discuss with the participant and record significant past medical history, including the duration of diabetes, and whether there is established cardiovascular disease, hypertension, or other significant medical history. At 6 and 12 months the CRN nurse or practice nurse will be asked to report any changes in the medication.

The nurse will measure and record weight in light clothing. S/he will record blood pressure, measured after 5 minutes seated, taking 3 measurements at least a minute apart. The nurse will ask participants to

complete questionnaires (PAID and WHO-5). The nurse will also either take or arrange for blood tests to be taken to measure HbA1c, lipid profile, and in people with established cardiovascular disease CRP. These tests will include the tests necessary for FIB-4 (liver function tests, aspartate transaminase (AST), full blood count). 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.

9.7. Follow-up Visits in both arms

First follow-up visit

This will take place at six months. Practice staff will record weight, take or appraise the patients' own records of blood pressure, and take or arrange for blood tests to measure HbA1c, liver function tests, full blood count, and AST. The latter three measures are for FIB-4. Participants will also be asked to complete questionnaires as undertaken at baseline. Participants in the intervention group will be asked to complete a questionnaire about their experience of the intervention.

Second follow-up visit

This will take place at 12 months. Practice staff will repeat all measures obtained at the baseline assessment including the participant-completed questionnaires (but excluding height). Additionally, the practice staff will record the occurrence of all serious adverse events that have occurred, most commonly hospitalisations and classify these as diabetes related (macrovascular disease, microvascular disease), and other.

Long-term follow-up

We will ask participants to agree to flagging of their records by NHS Digital and will extract data from the National Diabetes Audit on weight, HbA1c, blood pressure, lipids, and the occurrence of macrovascular and microvascular disease.

9.8. Sample Handling

Blood samples will be taken at the 3 specified visits. All blood samples will be taken, handled, analysed and disposed of according to standard NHS procedures and local practice policy. Blood samples will be taken according to the study schedule outlined in appendix B, in order to estimate changes in glycaemic control and other biomarkers. The samples will be sent to NHS laboratories for analysis and results reported to the GP following standard procedures. These data will subsequently be extracted from participants' medical records onto the participant CRF.

9.9. Therapeutic visits in intervention arm only

In the intervention group only, participants will in addition see the practice nurse (or suitably qualified practice staff) as detailed in 9.5.1. At such visits, the nurse will record that s/he has delivered the intervention and assess and record the patient's adherence to the programme and whether there have been symptomatic episodes of hypoglycaemia that required outside assistance or symptomatic hypotension.

As part of appropriate clinical care, s/he may measure blood glucose or blood pressure and may, with medical input, decide on medication changes. Any medication changes for hypertension or for glycaemic control will be recorded in the CRF.

9.10. Qualitative interviews in the intervention arm

We aim to assess the impact of the programme on the everyday lives of participants randomised to the DIAMOND programme and how the support was experienced 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, baseline dietary preferences (e.g. vegetarian) and weight loss outcomes. 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 telephone the participant to arrange and then conduct an interview 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 on the participant's diabetes. All telephone interviews will be audio-recorded.

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, reassuring the participant that their healthcare providers will not hear their views. Topics will include: their experience of weight and diabetes management before, during and immediately after the study intervention period, and of the intervention itself; whether they self-report a current weight loss or dietary change attempt, and what types of methods are being employed. They will also explore in more depth, preliminary themes generated during pilot qualitative data collection following the feasibility study and follow up cohort study, including: perceptions of the DIAMOND programme as a "diet" vs a "lifestyle change" and its sustainability; the role of external vs internal motivation for health behaviour change in this population; and unintended consequences of engagement with the programme (for example any change in other health behaviours (e.g. exercise), and changes in beliefs (e.g. understanding of and models of obesity)). Where possible and where agreed, we will interview participants up to three times during the year of their initial participation; early in the programme, in the later maintenance stage (after 12 weeks), and after the end of support (after 26 weeks).

For further details on data recording and record keeping for telephone interviews, please refer to Section 12.3

9.11. Early Discontinuation/Withdrawal of Participants

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 adhere to study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Participants may also withdraw from active follow-up and further communication but allow the study team to continue to access their medical records.

In addition, the clinical team or trial team may advise the participant to cease treatment on the DIAMOND programme if it is considered necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Clinical decision for other reasons

Follow-up of participants will be unaffected by withdrawal from treatment.

Participants who withdraw from treatment or follow-up will be analysed as allocated, with missing data specified in Section 11. Participants who withdraw will not be replaced.

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

9.12. Definition of End of Study

The end of active follow-up is the final data capture of the participant's notes review at 12-month follow-up. However, we will seek consent for follow-up in perpetuity with NHS Digital linkage through the National Diabetes Audit and therefore this element of the study will continue for the foreseeable future.

10. SAFETY REPORTING

We considered but decided to not record adverse events, except adverse events of special concern (see below). It is hard to engage people who are receiving no intervention (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 12 months, we will record serious adverse events from the medical records 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 DiRECT, 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.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death

- is life-threatening
- 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.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator 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 should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

A full statistical analysis plan will be prepared before database lock and finalised before any analysis takes place, which will be posted in a public registry.

11.2. Description of the Statistical Methods

We will analyse the primary and other outcomes using a three-level mixed effects generalised linear regression models with appropriate link functions for binary data and for continuous data using an identity link function. The model, where appropriate, will include data measured at repeated time points, adjusting for minimization factors (ethnicity and socioeconomic status), and baseline measure. The model will include practice as a random effect as well as each participant to account for the repeated measures on the same participant and an interaction term for the treatment by time interaction to allow the treatment effect to differ at each time point. The model will allow that the standard deviation may differ between trial arms, as we expect the SD to be larger in the intervention than control group, based on previous trials. For the primary outcome, people lost to follow-up will be assumed not to have achieved remission, although people who have died will be excluded from the denominator. For the secondary outcomes, we will adjust for baseline measurement and assume data are missing at random. Thereafter, we will conduct sensitivity analyses assuming a range of outcomes for those missing from follow-up, using a procedure developed by White and colleagues for informative imputation of the primary outcome, where missingness is probably related to outcome using pattern mixture models[47, 48].

For outcomes beyond one year, we will use mixed effects models to allow repeated measures of these outcomes at variable times as these outcomes are measured at routine annual reviews for people with diabetes, whether in remission or not.

11.3. Sample Size Determination

We assume 4% of control group participants will be in remission at 1 year and that an increase to 15% for a low intensity and low-cost intervention would represent a valuable outcome to patients. Our PPI groups valued any increase in remission and, based on modelling of the DiRECT trial, this is likely to be cost-effective and possibly cost-saving for the NHS. A weight loss difference of around 5kg should be sufficient to achieve this, but we are planning for greater weight losses with our intervention. With 93.5% power and a 5% 2-sided significance, 376 participants would be needed in an individually randomised trial. In DiRECT, the ICC for remission was <0.01. With 9 participants per practice, the cluster design effect would be 1.08, inflating the sample to 406 participants; adjusted for 20% loss to follow-up gives 508 participants. This would necessitate recruiting 56 practices. This sample size would give adequate power to detect this difference in remission and most other secondary outcomes.

For the secondary outcomes (defined below), the power with the proposed sample size is as follows:

Secondary outcomes	Difference worth detecting	SD of change	ICC	Design effect	Coefficient of Variation	Power
HbA1c	5 mmol/mol	13	0.01	1.08	2.6	70%
Systolic BP	5 mmHg	18	0.08	1.64	3.6	-
Diastolic BP	3 mmHg	11	0.01	1.08	3.7	16%
TC/HDL ratio	0.2	0.35	0.01	1.08	1.8	98%
Cardiovascular risk (QRISK/SMART)	1%	2.5	0.01	1.08	2.5	74%
Wellbeing score	2	0.9	0.01	1.08	0.5	>95%
PAID score	5 points	7	0.01	1.08	1.4	>95%

The estimates of ICC and SD of change are derived mainly from the DiRECT and DROPLET trials.

We will invite participants to take part in interviews or group discussions until we reach data saturation.

11.4. Analysis populations

The primary analysis population will include all randomised participants, as defined by protocol eligibility criteria, regardless of what intervention they actually received or compliance of intervention. Other analysis populations will be pre-specified in the SAP.

11.5. Decision points

We have allowed 14 months to recruit participants overall and 4 months for the pilot phase, scheduling recruitment at half the monthly rate (39/month) over the first two months followed by 12 months at full recruitment. Recruitment draws from an existing pool of patients, rather than waiting for new cases to occur, so full recruitment requires opening sites and for these sites to identify, screen, and write to

potential participants, and the CRN to hold recruitment clinics at the practice. The internal pilot will be assessed at 4 months using the following criteria:

	Red	Amber	Green
Trial recruitment compared with target (117 participants)	<60%	60-99%	≥100%
Total number of participants recruited	<70	70-116	≥117
Number of sites opened	<10	10-14	≥15
Mean number of participants recruited/ site	<5	5-8	≥9
Site recruitment	<7	7-12	≥13
Proportion attempting intervention (lower 95%CI)	<50%	50-59%	60%
Cluster size standard deviation	≥8	5.1-7.9	≤5

We will progress if the trial achieves mainly green or amber and stop if the trial achieves mainly red ratings. The final decision will rest with the Trial Steering Committee (TSC).

11.6. Stopping rules

There are no formal stopping rules other than for failure to meet targets as described in Section 11.5 and at the discretion of the HTA, advised by the TSC.

11.7. The Level of Statistical Significance

A 2-sided 5% level of significance will be used for the primary and secondary outcomes.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be reported, with reasons where available, and the missing data mechanism explored. Although, the mixed effect model implicitly accounts for data missing at random (MAR). Additional sensitivity analysis will be carried out to explore the mechanisms of missingness.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

We will report all such deviations in the papers that report these analyses.

11.10. Health Economics Analysis

We consider it is important to include a cost-effectiveness analysis from the health and social care perspective since commissioning decisions are made on this basis. There is good reason to believe that if the trial finds evidence of a difference in remission rates it will be cost effective since the cost (approximately £100) is a fraction of the cost of TDR (£1400).

We also considered whether to include a within-trial analysis and decided against this. Type 2 diabetes diagnosed within six years does not usually cause decrements in quality of life, as measured by typical measures such as EQ5D, which measure people's ability to perform the tasks of daily living unhindered by pain and depression. Nor is it likely that remission would change such scores. Instead, the threat of type 2 diabetes is that it will lead to macrovascular and microvascular disease that, over the longer term, erodes quality of life, shortens life expectancy, and increases costs to the NHS. The primary benefit of diabetes remission is that such events are prevented or pushed into the future. Thus, a within-trial analysis does not tell people with diabetes about their future risk, nor does it inform commissioning of services such as this, which are an investment in the prevention of future ill-health. We therefore decided that the relevant approach was to model these future benefits against upfront costs, to assess the outcomes of return on investment, cost-effectiveness, and whether in fact the programme is cost-saving, as is projected for TDR for diabetes remission[49].

We will use the NIHR School for Public Health Research (SPHR) Diabetes Prevention Model[50, 51] to estimate the impact of diabetes remission, cardiovascular incidence and complications of diabetes in adults and impact on length and quality of life and the NHS costs compared with usual care. We will examine the equity impact of this programme and cost-effectiveness in population subgroups. The SPHR microsimulation model uses statistical modelling of risk factors for diabetes and cardiovascular disease (including body mass index, blood pressure, cholesterol and HbA1c) to simulate individual trajectories over a lifetime based on longitudinal analysis of the Whitehall II cohort and the UKPDS HbA1c trajectories for individuals with type 2 diabetes. The simulation population will be described by the baseline characteristics of the trial participants and missing data will be imputed based on nationally representative sources, such as the Health Survey for England. The individual's risk factors are used to estimate the occurrence of complications of diabetes, congestive heart failure, cardiovascular disease, cancer, osteoarthritis, dementia and depression. The risk of diabetes related complications is described by HbA1c on a continuous scale which extends to pre-diabetic health states. Therefore, the model is well suited to estimate the cost-effectiveness of interventions achieving diabetes remission. Changes in BMI, Hba1c, systolic blood pressure, HDL cholesterol and LDL cholesterol for the DIAMOND intervention at 12 months will be implemented in the model. Over subsequent years, the initial effect on risk factor trajectories will be assumed to decrease in line with observations from the DiRECT trial and expert opinion about the duration of effects. We will assume that individuals will have a higher risk of type-2 diabetes diagnosis after remission and formal expert elicitation will estimate the magnitude of this effect and uncertainty.

The analysis will adopt an NHS and personal social services perspective. The intervention costing process will include the costs of developing and delivering the online training for nurses separately from the costs of delivering the programme. The costs of printed resources, and professional staff time to deliver the programme will be estimated from the schedule of nurse visits delivered to describe the roll out costs of the intervention. Unit costs for professional staff will be obtained from nationally representative sources. The costs of usual care will account for the costs of other diabetes education or weight management

programmes attended. Costs and Quality Adjusted Life Years (QALYs) will be discounted at 3.5%[52]. Probabilistic sensitivity analysis (PSA) will describe the uncertainty and the base case analysis will describe the mean incremental costs and incremental QALYs to describe the cost-effectiveness of the intervention compared with usual care from the PSA. Additional sensitivity analysis will explore the impact of key model parameters on the cost-effectiveness of the intervention; including the effect of adherence to the programme, and diabetes relapse.

We considered but ultimately decided against including an analysis of cost from the participants' perspective. This is an important question, because there is a broad perception that healthier foods cost more. However, to assess this properly would require linkage to food purchasing data including information of type and location of stores since prices vary. No efficient system exists to do so at the present time. However, as part of the BRC we are working to be able to attribute costs, based on prices in the UKs largest retailer as offered on their website, and this may allow us to estimate average diet costs in each group.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. 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), laboratory records.

CRF entries will be considered source data where 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.

12.2. 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.

12.3. Data Recording and Record Keeping

The participant telephone interviews will be audio recorded (with participants' consent). Each recording will be pseudonymised by patient ID recorded at the beginning, 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.

Anonymised intervention group participant experience questionnaires will be completed via a JISC online survey 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.

All trial data will be entered online into REDCap. 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.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

On completion of the trial and once all study activity has been completed, the trial documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for five years. Identifiable information of participants who consented to long-term follow up will be stored for the duration of long-term follow-up. Any identifiable information of participants not consenting to long-term follow-up, will be destroyed at the end of the trial.

Prior to database lock, the Data Manager will undertake a dataset review. The anonymised dataset will be stored on a University secure server with access held by the archivist as per PC-CTU_SOP_TM124. Procedures in relation to data transfer are documented within the PC-CTU_SOP_DM108 and in accordance with the Information Governance Policy.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. 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. Specifics will be detailed in the trial Risk Assessment and Monitoring Plan.

13.3. Study Committees

An independent trial steering committee (TSC) will provide oversight of all matters relating to participant safety and data quality. The TSC will include at least one independent clinician, an independent statistician

and a participant representative. The TSC will be asked to review the trial protocol and will provide expert advice to the Trial Management Group (TMG) on the trial progress.

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

14. 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.

15. 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 CI, 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.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

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

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

16.4. Other Ethical Considerations

This study involves no identified significant risks to participants. They are primarily consenting to engaging with dietary and behavioural advice which is intended to support them to lose weight and improve their diabetes control and general health. There are known no significant risks of this advice. However, participants may experience constipation when changing diet. Advice will be provided to prevent this and/ or treatment provided should participants experience constipation.

Venepuncture for blood samples may cause momentary discomfort. Standard NHS operating procedures as used in routine clinical care will be used for the collection and processing of samples, and all will be carried out by appropriately trained clinicians in the participants' usual GP practice. In practices providing the intervention, we will ask clinicians to withdraw medication for hypertension and diabetes following the protocols used for the NHS Diabetes Remission Programme i.e. on starting the DIAMOND programme and also to ask patients to inform their local warfarin monitoring service, who may advise an additional blood test.

We will access data through NHS Digital for 20 years beyond the end of the initial study period. Only the minimum required data will be used. All data will be stored securely in an online database (password protected and on a secure server). The database will be pseudonymised and a secure digital storage containing the link between identification number and participant identifiable information will be stored in a secure archiving facility.

16.5. 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, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. 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 date as specified on the end of trial declaration.

16.7. Participant Confidentiality

The study will comply with the UK
General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

For University of Oxford sponsored studies please refer in particular to the University of Oxford's:
Data Protection Checklist https://researchsupport.admin.ox.ac.uk/policy/data/checklist
Practical Considerations https://researchsupport.admin.ox.ac.uk/policy/data/practical

16.8. Expenses and Benefits

In recognition of the lack of benefit for attending for assessment of study outcomes, participants will receive a £20 voucher for attending their 6 months visit and a £20 voucher for attending for 12-month follow-up in the form of vouchers.

17. FINANCE AND INSURANCE

17.1. Funding

Research funding is provided by the National Institute for Health Research Health Technology Assessment Programme. Costs for long-term follow up through NHS Digital are low and funding will be covered by the team.

17.2. 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.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. 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-HTA. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. 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 University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

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

21. REFERENCES

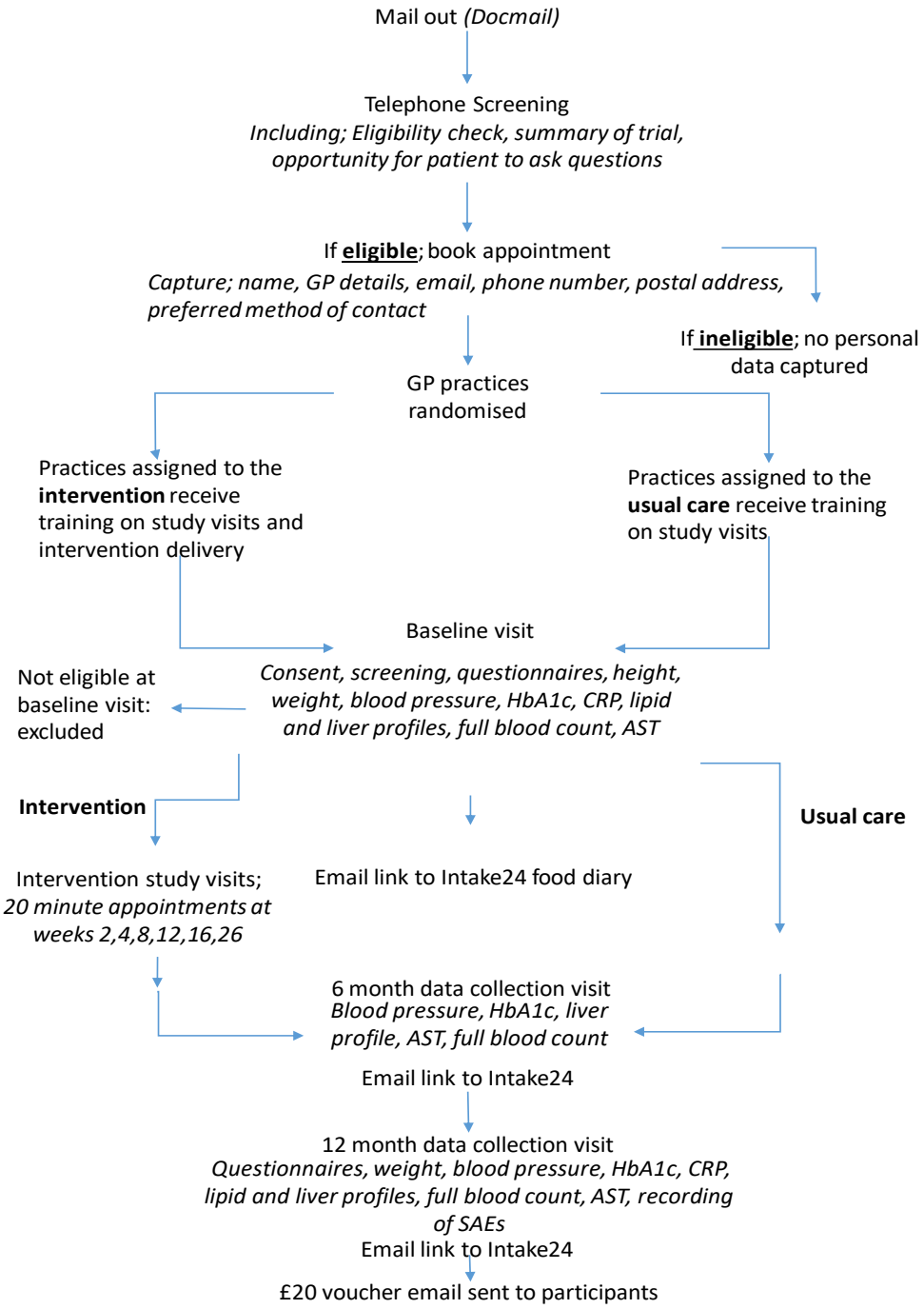
1. NICE. Type 2 diabetes in adults: management. 13/01/21, 2021. Updated 16/12/20. Accessed 13/01/21, 2021. https://www.nice.org.uk/guidance/ng28/chapter/Recommendations
2. Green AJ, Bazata DD, Fox KM, Grandy S, Group ftSS. Health-related behaviours of people with diabetes and those with cardiometabolic risk factors: results from SHIELD. 2007;61(11):1791-1797. doi:https://doi.org/10.1111/j.1742-1241.2007.01588.x
3. Aveyard P, Lewis A, Tearne S, et al. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *Lancet (London, England)*. Nov 19 2016;388(10059):2492-2500. doi:10.1016/s0140-6736(16)31893-1
4. Audit ND. *Report 1 - Care Processes and Treatment Targets 2018-19, Short Report*. Report. NDA; 2019. *National Clinical Audit and Patient Outcomes Programme (NCAPOP)*. 1. 13/12/2019. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1--care-processes-and-treatment-targets-2018-19-short-report
5. Booth HP, Prevost AT, Gulliford MC. Access to weight reduction interventions for overweight and obese patients in UK primary care: population-based cohort study. 2015;5(1):e006642. doi:10.1136/bmjopen-2014-006642 %J BMJ Open
6. Buchwald H, Estok R, Fahrbach K, et al. Weight and Type 2 Diabetes after Bariatric Surgery: Systematic Review and Meta-analysis. *The American Journal of Medicine*. 2009/03/01/ 2009;122(3):248-256.e5. doi:https://doi.org/10.1016/j.amjmed.2008.09.041
7. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The Long-Term Effects of Bariatric Surgery on Type 2 Diabetes Remission, Microvascular and Macrovascular Complications, and Mortality: a Systematic Review and Meta-Analysis. *Obesity surgery*. Oct 2017;27(10):2724-2732. doi:10.1007/s11695-017-2866-4
8. Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P. Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. Mar 2016;17(3):225-34. doi:10.1111/obr.12366
9. Leslie WS, Taylor R, Harris L, Lean MEJ. Weight losses with low-energy formula diets in obese patients with and without type 2 diabetes: systematic review and meta-analysis. *Int J Obes (Lond)*. 2017;41(1):96-101. doi:10.1038/ijo.2016.175
10. Astbury NM, Aveyard P, Nickless A, et al. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. 2018;362:k3760. doi:10.1136/bmj.k3760 %J BMJ
11. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet (London, England)*. Feb 10 2018;391(10120):541-551. doi:10.1016/s0140-6736(17)33102-1
12. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *The Lancet Diabetes & Endocrinology*. 2019;7(5):344-355. doi:10.1016/S2213-8587(19)30068-3
13. Thom G, Messow C-M, Leslie WS, et al. Predictors of type 2 diabetes remission in the Diabetes Remission Clinical Trial (DiRECT). n/a(n/a):e14395. doi:https://doi.org/10.1111/dme.14395
14. Morris E, Aveyard P, Dyson P, et al. Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND): protocol for a randomised feasibility trial. *BMJ Open*. Jan 17 2019;9(1):e026460. doi:10.1136/bmjopen-2018-026460

15. Morris E, Aveyard P, Dyson P, et al. A food-based low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: a randomised controlled feasibility trial. *Diabetes, obesity & metabolism*. Nov 10 2019;doi:10.1111/dom.13915
16. Hartmann-Boyce J, Theoodoulou A, Oke J, et al. Programme characteristics influencing weight change following behavioural weight loss: a systematic review and meta-analysis *In submission* 2021;
17. Hartmann-Boyce J, Theoodoulou A, Oke J, et al. Weight regain after behavioural weight management programmes and the impact on cardiometabolic risk factors, health outcomes, and quality of life: a systematic review with meta-analyses and health economic modelling *In submission*. 2021;
18. Kashef MA, Giugliano G. Legacy effect of statins: 20-year follow up of the West of Scotland Coronary Prevention Study (WOSCOPS). *Glob Cardiol Sci Pract*. 2016;2016(4):e201635-e201635. doi:10.21542/gcsp.2016.35
19. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ (Clinical research ed)*. Nov 14 2017;359:j4849. doi:10.1136/bmj.j4849
20. Hartmann-Boyce J, Johns DJ, Jebb SA, Aveyard P. Effect of behavioural techniques and delivery mode on effectiveness of weight management: systematic review, meta-analysis and meta-regression. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. Jul 2014;15(7):598-609. doi:10.1111/obr.12165
21. Samkani A, Skytte MJ, Kandel D, et al. A carbohydrate-reduced high-protein diet acutely decreases postprandial and diurnal glucose excursions in type 2 diabetes patients. *The British journal of nutrition*. Apr 2018;119(8):910-917. doi:10.1017/s0007114518000521
22. Skytte MJ, Samkani A, Petersen AD, et al. A carbohydrate-reduced high-protein diet improves HbA1c and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. *Diabetologia*. Nov 2019;62(11):2066-2078. doi:10.1007/s00125-019-4956-4
23. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med*. Mar 2013;30(3):267-75. doi:10.1111/dme.12039
24. SACN. *Scientific Advisory Committee on Nutrition, Lower carbohydrate diets for adults with type 2 diabetes*. Draft for consultation. 2020. Jan 2020 Accessed 13 Aug 2020. (8-19)
25. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *European journal of epidemiology*. Feb 2018;33(2):157-170. doi:10.1007/s10654-017-0352-x
26. Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis. *Diabetes research and clinical practice*. May 2018;139:239-252. doi:10.1016/j.diabres.2018.02.026
27. Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. *European journal of clinical nutrition*. Mar 2018;72(3):311-325. doi:10.1038/s41430-017-0019-4
28. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BMJ open diabetes research & care*. 2017;5(1):e000354. doi:10.1136/bmjdrc-2016-000354

29. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. *Diabetes research and clinical practice*. Sep 2017;131:124-131. doi:10.1016/j.diabres.2017.07.006
30. Fan Y DH, Chen G, Mao X, Liu C. Effects of low carbohydrate diets in individuals with type 2 diabetes: systematic review and meta-analysis. Journal. *Int J Clin Exp med*. 01 Sep 16 2016;9(6):9.
31. Naude CE, Schoonees A, Senekal M, Young T, Garner P, Volmink J. Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis. *PLOS ONE*. 2014;9(7):e100652. doi:10.1371/journal.pone.0100652
32. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *The American journal of clinical nutrition*. Mar 2013;97(3):505-16. doi:10.3945/ajcn.112.042457
33. Castaneda-Gonzalez LM, Bacardi Gascon M, Jimenez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. *Nutricion hospitalaria*. Nov-Dec 2011;26(6):1270-6. doi:10.1590/s0212-16112011000600013
34. Korsmo-Haugen HK, Brurberg KG, Mann J, Aas AM. Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. *Diabetes, obesity & metabolism*. Jan 2019;21(1):15-27. doi:10.1111/dom.13499
35. van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. *The American journal of clinical nutrition*. Aug 1 2018;108(2):300-331. doi:10.1093/ajcn/nqy096
36. McArdle PD, Greenfield SM, Rilstone SK, Narendran P, Haque MS, Gill PS. Carbohydrate restriction for glycaemic control in Type 2 diabetes: a systematic review and meta-analysis. *Diabetic medicine : a journal of the British Diabetic Association*. Mar 2019;36(3):335-348. doi:10.1111/dme.13862
37. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet (London, England)*. Feb 2 2019;393(10170):434-445. doi:10.1016/s0140-6736(18)31809-9
38. Larsen TM, Dalskov SM, van Baak M, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med*. Nov 25 2010;363(22):2102-13. doi:10.1056/NEJMoa1007137
39. Hjorth MF, Ritz C, Blaak EE, et al. Pretreatment fasting plasma glucose and insulin modify dietary weight loss success: results from 3 randomized clinical trials. *The American journal of clinical nutrition*. Aug 2017;106(2):499-505. doi:10.3945/ajcn.117.155200
40. Koutoukidis DA, Jebb SA, Tomlinson JW, Cobbold JF, Aveyard P. Association of Weight Changes With Changes in Histological Features and Blood Markers in Nonalcoholic Steatohepatitis. *Clinical Gastroenterology and Hepatology*. doi:10.1016/j.cgh.2021.03.047
41. Berners-Lee M. *How bad are bananas?: the carbon footprint of everything*. Profile Books; 2020.
42. Murphy M, Scott LJ, Salisbury C, et al. Implementation of remote consulting in UK primary care following the COVID-19 pandemic: a mixed-methods longitudinal study. *British Journal of General Practice*. 2021;71(704):e166-e177.

43. Ahern AL, Aveyard P, Boyland EJ, Halford JC, Jebb SA. Inequalities in the uptake of weight management interventions in a pragmatic trial: an observational study in primary care. 2016;66(645):e258-e263. doi:10.3399/bjgp16X684337 %J British Journal of General Practice
44. Graham J, Tudor K, Jebb SA, et al. The equity impact of brief opportunistic interventions to promote weight loss in primary care: secondary analysis of the BWeL randomised trial. *BMC Medicine*. 2019/03/01 2019;17(1):51. doi:10.1186/s12916-019-1284-y
45. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science : IS*. Apr 23 2011;6:42. doi:10.1186/1748-5908-6-42
46. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. 2005;14(1):26-33. doi:10.1136/qshc.2004.011155 %J Quality and Safety in Health Care
47. Mavridis D, White IR. Dealing with missing outcome data in meta-analysis. *Research synthesis methods*. Jan 2020;11(1):2-13. doi:10.1002/jrsm.1349
48. Tompsett D, Sutton S, Seaman SR, White IR. A general method for elicitation, imputation, and sensitivity analysis for incomplete repeated binary data. 2020;39(22):2921-2935. doi:https://doi.org/10.1002/sim.8584
49. Xin Y, Davies A, Briggs A, et al. Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the Diabetes Remission Clinical Trial (DiRECT)/Counterweight-Plus weight management programme. *Diabetologia*. 2020/10/01 2020;63(10):2112-2122. doi:10.1007/s00125-020-05224-2
50. Breeze PR, Thomas C, Squires H, et al. Cost-effectiveness of population-based, community, workplace and individual policies for diabetes prevention in the UK. *Diabetic medicine : a journal of the British Diabetic Association*. Aug 2017;34(8):1136-1144. doi:10.1111/dme.13349
51. Breeze PR, Thomas C, Squires H, et al. The impact of Type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. *Diabetic medicine : a journal of the British Diabetic Association*. May 2017;34(5):632-640. doi:10.1111/dme.13314
52. NIfHCE. Developing NICE guidelines: the manual. 2014;ISBN: 978-1-4731-0809-7.

22. APPENDIX A: STUDY FLOW CHART



23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures					
	Screening	**Baseline**	**6 month**	**12 month**	**Long-term follow up**
Eligibility checks	x	x			
Informed consent		x			
Demographics		x			
Medical history		x			
Intake24 (after visit via email)		x	x	x	
Questionnaires (PAID, WHO-5)		x		x	
Blood pressure		x	x	x	
Height		x			
Body weight		x	x	x	
HbA1c, CRP, lipid profile, liver profile, AST, full blood count		x		x	
HbA1c, liver profile, AST, full blood count			x		
Intervention visits (intervention group only)			*		
Intervention group questionnaire (intervention group only)			*		
NHS Digital patient notes					x

* Six visits within the first six months on the discretion of the site staff (suggested weeks 2, 4, 8, 12, 16, 26)

24. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.0	16/05/2022	Dr J H Scragg	No changes made to protocol. Changes only made to include participating sites within Wales and to streamline intervention materials.
2	1.1	24/08/2022	Dr J H Scragg	Correction of minor typographical errors. Inclusion of a study within a programme (SWAP) and inclusion of two new exploratory outcomes to reflect the SWAP.
3	1.2	15/12/2022	Dr J H Scragg	Expansion of planned exploratory subgroup analyses. New questionnaire incorporated at 6 months as part of qualitative substudy. Expansion of intervention materials.