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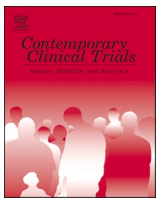

Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND) in primary care: A protocol for a cluster randomised trial

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ABSTRACT

Introduction: There is strong evidence that type 2 diabetes (T2D) remission can be achieved by adopting a low-energy diet achieved through total dietary replacement products. There is promising evidence that low-carbohydrate diets can achieve remission of T2D. The Dietary Approaches to the Management of type 2 Diabetes (DIAMOND) programme combines both approaches in a behaviourally informed low-energy, low-carbohydrate diet for people with T2D, delivered by nurses in primary care. This trial compares the effectiveness of the DIAMOND programme to usual care in inducing remission of T2D and in reducing risk of cardiovascular disease.
Methods and analysis: We aim to recruit 508 people in 56 practices with T2D diagnosed within 6 years, who are demographically representative of the UK population. We will allocate general practices, based on ethnicity and socioeconomic status, to provide usual care for diabetes or offer the DIAMOND programme. Participants in practices offering DIAMOND will see the nurse seven times over 6 months. At baseline, 6 months, and 1 year we will measure weight, blood pressure, HbA1c, lipid profile and risk of fatty liver disease. The primary outcome is diabetes remission at 1 year, defined as HbA1c $<$ 48 mmol/mol and off glucose-lowering medication for at least 6 months. Thereafter, we will assess whether people resume treatment for diabetes and the incidence of microvascular and macrovascular disease through the National Diabetes Audit. Data will be analysed using mixed-effects generalised linear models.
This study has been approved by the National Health Service Health Research Authority Research Ethics Committee (Ref: 22/EM/0074).
Trial Registration number: ISRCTN46961767.

1. Introduction

Type 2 diabetes (T2D) was, until recently, thought to be a chronic and progressive condition and optimising glycaemic control using pharmaceutical agents was the mainstay of T2D management. However, there is now strong evidence to show that weight loss induces remission of T2D.

The Diabetes Remission Clinical Trial (DiRECT) and Diabetes Intervention Accentuating Diet and Enhancing Metabolism-I (DIADEM-I) trials randomised participants with new onset T2D to either a ~ 800 kcal/day total diet replacement programme (TDR) with support or usual care (no weight loss intervention) [1,2]. Co-primary outcomes in DiRECT were the proportion of participants achieving remission of T2D (defined as HbA1c $<$48 mmol/mol after at least 2 months off all anti-diabetic medications, from baseline to 12 months) and reduction of weight of $\geq$15 kg at 1 year. The primary outcome in DIADEM-I was

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weight loss at 1 year. Average weight loss at 12 months in DiRECT and DIADEM-I were 10.0 kg and 11.98 kg in the intervention group and 1.0 kg and 3.98 kg in the control group (adjusted mean differences −8.8 kg [95% CI −10·3 to −7·3; $p < 0{\cdot}0001$] and − 6.08 kg [95% CI −8·37 to −3·79, $p < 0{\cdot}0001$]), respectively. Both programmes were delivered with evidence of safety, adverse effects were mild and the majority of people assigned to TDR persisted with the programme. DiRECT showed that 46% of people randomised to the intervention went into remission at one year compared with 4% in the control group, (odds ratio (OR) 19·7 (7·8 to 49·8)), and at two years corresponding figures were 36% and 3%, OR 25·8 (8·3 to 80·8) [3]. The probability of remission was linearly associated with weight lost, and weight loss was the only meaningful predictor of remission [4]. In DIADEM-I, 61% of participants who received the intervention went into remission at one year, compared with 12% of the usual care group (OR 12·07 (3·43 to 42·45)).

However, this approach is not universally acceptable to patients. In DiRECT, 28% of potentially eligible people offered TDR agreed to enrol, following invitation from their GP practice. Of these, 72% were confirmed eligible at the screening appointment, meaning only 20% overall participated [5]. A recent single primary care setting study in Australia ($n = 153$), offered a partial meal replacement (two food replacement meals and one food-based), 51(33%) started the intervention and 34(67%) completed it [6]. Alternative approaches to treatment may increase the proportion of the population who can benefit.

Emerging evidence suggests that low carbohydrate diets may be a promising strategy for diabetes remission [7]. A review found a significant reduction in the risk of diabetes at 6 months (risk difference 0·32 (0.17 to 0.47); 8 studies, $n = 264$, $I^2 = 58\%$), though 12-month data were sparse. Within a single primary care setting in England, low-carbohydrate dietary advice has been shown to significantly reduce weight (99.7 (IQR 86.2 to 109.3)kg to 91.4 (IQR 79 to 101.1)kg, $p < 0.001$) and HbA1c (65.5 (IQR 55 to 82)mmol/mol to 48 (IQR 43 to 55) mmol/mol, $p < 0.001$) in people with T2D [8]. Additional to weight loss, there may be specific benefits of low-carbohydrate diets by reducing post-prandial glucose excursions and liver and pancreatic fat which may restore insulin sensitivity and secretion in the absence of weight loss [9,10]. The Scientific Advisory Committee on Nutrition (SACN) review of reviews of the effects of low-carbohydrate diets in T2D found no difference in weight loss or Hba1c at one year compared to diets with a higher carbohydrate content, but concluded that trials of the long-term effects of low-carbohydrate diets in T2D were needed [11]. Further, about 20% of people with T2D and obesity also have non-alcoholic fatty liver disease (NAFLD). There is evidence that weight loss may be effective to reduce the risk or severity of NAFLD [12,13].

We conducted a feasibility trial of the intervention (DIAMOND; Dietary Approaches to the Management Of type 2 Diabetes). We emulated the low-energy diet (800-1000 kcal/day) approach using real food over eight weeks with a weight loss maintenance for four weeks thereafter, focussing on reducing energy from carbohydrate foods, based on evidence that the weight loss relative to control was proportional to the difference in energy prescription [14]. Nurses delivered low intensity behavioural support and participants had extensive written materials. It passed all feasibility criteria comfortably; recruitment, acceptance of the intervention, adherence by nurses, and follow-up. Mean weight loss and reduction in HbA1c in the intervention group was 7.5 kg (95% CI –11 to -4 kg) and 15.7 mmol/mol (95% CI -24.1 to −7.3 mmol/mol) greater than usual care, respectively [15]. However, we do not know if these clinical changes can be sustained over a longer period or if this could be an effective approach to achieve remission of T2D.

1.1. Aim

The aim of the DIAMOND study is to assess whether a low-energy, low-carbohydrate diet (800-1000 kcal/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. We will assess these outcomes over the longer-term through linkage through National Diabetes Audit by NHS Digital.

2. Methods

2.1. Design and setting

The study will take place in general practices in England and Wales. It is a pragmatic, cluster-randomised, two-arm parallel-group trial with the primary endpoint as objectively measured remission of T2D between 6 and 12 months. Due to the nature of the intervention, it is not possible to blind participants, clinicians, or some of the study team to the treatment allocation after randomisation. In the feasibility trial, there was evidence of contamination, so we have elected to use cluster-randomisation for this trial. We will conduct an internal pilot assessment 4 months from the onset of recruitment, with criteria based on practice and participant recruitment, cluster size and cluster size standard deviation.

2.2. Recruitment of general practices

All practices in England and Wales will be eligible but we will create a quota of practices that represent the socioeconomic profile of England and Wales based on a measure of deprivation (index of multiple deprivation (IMD)) and ethnicity of the practice population, measured by percentage non-white. We will assess these characteristics of practices as they enrol, and will cease enrolling practices once the quota is filled. This will facilitate recruitment of a population that represents the population of England and Wales.

2.3. Patient recruitment

We aim to enrol adults with T2D diagnosed in the past six years and with a BMI $\geq$27 kg/m^2 and who may benefit from achieving remission. These criteria match those of DiRECT and the National Health Service (NHS) T2D remission programme in England. The inclusion and exclusion criteria are described in Table 1.

GPs will search their medical records for potential participants and exclude patients for whom the invite would be inappropriate. Practices will invite patients by letter, text message and/or phone calls. We will

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
• Participant is willing and able to give informed consent for participation in the study
• Adults (aged 18–70 years (inclusive)) with T2D diagnosed in the past six years
• BMI of at least 27 kg/m^2 and who may benefit from achieving remission, as determined by their GP
• Able to attend all intervention and research study visits to the practice and engage with all components of the intervention, such as self-monitoring blood glucose and blood pressure
• Participant is registered at a GP practice that is open for recruitment and randomised
Exclusion criteria
• Diagnosed with T2D but in remission using the NHS diabetes remission criteria
• Currently using insulin
• 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, planning pregnancy or breastfeeding
• Diagnosed with a recent myocardial infarction or stroke in the past three months or uncontrolled cardiac conduction abnormalities
• People with HbA1c $\geq$ 87 mmol/mol
• People with significant life-limiting illnesses that mean that remission is unlikely to improve health, other current severe illness or planned major surgery where 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

financially support practices to call selected patients to boost representation from typically under-represented groups, by reimbursement for staff time taken to identify and telephone patients. We have previously found that recruitment by letter alone leads to higher uptake by more affluent people [16], while in-person offer leads to higher take-up by the less affluent [17].

2.4. Study within a project

We are conducting methodological research on more environmentally sustainable ways to recruit participants. Since the COVID-19 pandemic, UK general practices have easy access to text messages. Recruiting by text reduces resource use. We will randomise practices to recruit by text or letter and compare response rate and the profile of participants. If recruitment falls short after the initial invite, practices will swap from text to letter or vice-versa and telephone potential participants if necessary to increase participation. We will ask practices to report anonymous data on the demographic and socioeconomic characteristics of invited patients.

2.4.1. Participant flow

The trial team will outline the nature of the study,its requirements and respond to patients' questions. If the patient is interested in participating, the trial team will check eligibility and book an appointment for a baseline visit at their GP practice, where eligibility will be confirmed. We aim to have an equal cluster size of around 9. We will book a quota of baseline visits and place later participants on a waiting list, inviting them to a visit if insufficient participants are enrolled.

Once eligibility is confirmed participants will be enrolled. Participants enrolled at GP practices randomised to deliver the DIAMOND programme will see practice nurses for two hours of support over seven appointments (weeks 0, 2, 4, 8, 12, 16 and 20) over 6 months. Nurses offering the DIAMOND programme will provide behavioural support and safety monitoring plus comprehensive resources, co-developed with people with diabetes.

2.5. Informed consent

All participants will be required to give informed consent before entry into the study, using an electronic form at the baseline appointment.

2.6. Baseline appointment

The Clinical Research Network (CRN) nurses are trained research nurses. The CRN nurse (or equivalent) will use medical and participants' reports to record significant past medical history, including the duration of diabetes, and whether there is established cardiovascular disease or hypertension. All medication and items required to determine cardiovascular risk score using QRISK2 and SMART will be recorded and checked against the participants' medical records.

The CRN nurse will measure weight, height, blood pressure and ask participants to complete questionnaires to assess diabetes distress (Problem Areas in Diabetes (PAID)) and mental wellbeing (WHO-5). The PAID questionnaire has high internal reliability in people with T2D, correlates with HbA1c, and has been validated in people with T2D [18]. The WHO-5 questionnaire has been shown to have good reliability and validity in people with T2D and obesity [19]. Height and weight will be measured to the nearest 1 cm and 0.1 kg using stadiometers and electronic scales available in the GP practices. Seated blood pressure will be measured in triplicate with 1 minute between measures.

A venous blood sample will be collected, to be analysed for glucose, HbA1c, HDL and LDL cholesterol, triglycerides, full blood count, AST, ALT and CRP. ALT and AST are used to determine Fib-4 score and CRP to determine the SMART score, where appropriate. All blood samples will be taken, handled, analysed and disposed of according to NHS procedures and practice policy. The samples will be sent to NHS laboratories for analysis and results reported to the GP following standard procedures. These data will be extracted from medical records onto the participant electronic case report form (eCRF).

Participants not on diabetes medication and whose HbA1c at baseline is <48 mmol/mol based on most recent medical records will be ineligible.

2.7. Follow-up visits in both arms

2.7.1. First follow-up visit

This will take place at six months. Practice staff will repeat all measures obtained at the baseline assessment, excluding height and reporting changes in medication. Participants in the intervention group will be asked to complete a questionnaire about their experience of the intervention.

2.7.2. Second follow-up visit

This will take place at twelve months. Practice staff will repeat all measures obtained atsix months and any changes in medication. Practice staff will record the occurrence of all serious adverse events (SAEs) that have occurred, most commonly hospitalisations, to assess whether these are diabetes related and, if so, classify whether they are macrovascular disease, microvascular disease or other complication.

On the day of each research study visit, and the subsequent day, participants will be asked to complete an online 24-h dietary recall questionnaire using Intake24.org [20].

2.7.3. Long-term follow-up

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

2.7.4. Intervention study visits

In the practices delivering the intervention, participants will, in addition, see the practice nurse seven times. Here, the nurse will record in the eCRF that they delivered the intervention 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. Online prompts are embedded within the eCRF and nurses will be provided with paper prompt forms to ensure that all components of the intervention are delivered. Medication changes for hypertension or for glycaemic control will be recorded in eCRFs.

2.8. Intervention

The DIAMOND programme is a behaviourally informed low-energy, low-carbohydrate diet delivered by practice staff in primary care. It draws on the motivational value of the relationship between the clinician and the patient for delivery and to provide behavioural support and provides technical knowledge through structured materials such as meal plans, addressing professionals' uncertainties [21].

The DIAMOND programme is a low-energy low-carbohydrate diet (800-1000 kcal with a maximum of 40-60 g carbohydrate/day, compared to usual intake of 200-250 g). The core principles include advice to exclude sugary and starchy foods except limited dairy and fruit, portion control and avoiding energy-dense foods. The maintenance programme supports transitioning to a sustainable dietary regimen to control energy intake, providing ~125 g/d carbohydrate, less than half the average population intake. It is based around the principles of the "3Rs": refrain (from high sugar foods), restrict (frequency and portions of starchy carbohydrates), and replace (swap to high-fibre varieties of carbohydrate).

Nurses offering the DIAMOND programme will provide two hours of support in seven face-to-face appointments over six months plus

comprehensive written support resources, co-developed by people with diabetes. The nurse will discuss the participant's health goals and how remission may achieve these. They will see participants at 0, 2, 4, 8, 12, 16 and 20 weeks from the start of the programme, responding flexibly to participants' needs, as in routine care. Appointments are 15–20 minutes long up to week 12 and 10 minutes thereafter.

We will provide online clinician training to support intervention delivery. This training will be provided following randomisation. Clinicians will be offered support throughout the intervention, and will be able to consult with the study team. Clinicians will be offered a supplementary online training session as their participants begin the weight maintenance phase. Behavioural analysis of existing qualitative literature and qualitative findings from the feasibility study identified critical domains of the Behaviour Change Wheel and Theoretical Domains Framework [22,23] to promote successful behaviour change in the healthcare professional delivering the intervention and facilitate effective delivery of the programme. Using these frameworks, influencing factors which the training targets are: psychological capability (knowledge and skills– explaining the scientific rationale for this approach, evidence of effectiveness, dietary principles, and training in brief motivational and behaviour change techniques for consultations), social and physical opportunity (structured dedicated intervention sessions to facilitate comprehensive, efficient delivery), and reflective motivation (sharing experiences of clinicians involved in the feasibility study describing how seeing the changes in their patients improved their motivation to engage, and the changes they could expect to see). Process analysis of the feasibility study highlighted the positive impact of providing checklists for intervention sessions, to ensure core concepts and actions were covered. Structured patient materials were designed to contain most core knowledge required for the programme, which could be used independently by patients but also for signposting during consultations, serving as prompts and giving the clinician confidence that they needed minimal specialist dietary knowledge to support patients undertaking the intervention.

We will ask clinicians in practices allocated to deliver the DIAMOND programme to withdraw medication for hypertension and diabetes, to minimise the risk of hypoglycaemic and hypotensive events following the protocols used for the NHS Diabetes Remission Programme. Clinicians will advise participants to stop taking these medications on their first day of the DIAMOND programme and for patients to inform their local warfarin monitoring service where applicable. Participants prescribed two medications for T2D will have all diabetes medicines withdrawn, and those prescribed $\geq$3 diabetes medications will have all medication withdrawn except metformin or similar medication that does not cause hyopglycaemia or risk ketoacidose), including sulphonylureas, meglitinides, and SGLT2 inhibitors [24]. Clinicians will ask participants with controlled blood pressure (systolic $<$140 mmHg and diastolic $<$90 mmHg) to reduce antihypertensive medications, withdrawing one medication used solely used for hypertension management, removing the one prescribed most recently. Participants will be advised to measure and record their BP and fasting blood glucose twice/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. As part of ongoing care, the nurse will review participants' home blood glucose and blood pressure measures and may decide on medication changes throughout the intervention, reintroducing medications where necessary.

2.9. Comparator

We aim to compare the DIAMOND intervention to current usual care for people with diabetes. While "usual care" includes 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 without specific support for weight loss, though people with T2D are encouraged to achieve a healthy weight and adhere to population diet and physical activity guidance.

Participant flow through the study is outlined in Fig. 1. Fig. 2 summarises the measurements collected.

2.10. Qualitative substudy

We aim to assess the impact of the programme on the lives of participants randomised to the DIAMOND programme, and how the support was experienced, through longitudinal semi-structured interviews. We will interview participants up to three times during the year of their participation; early in the programme, in the later maintenance stage (after 12 weeks), and after the end of support (after 26 weeks). We will ask all participants to consent to interview at baseline. This will be optional, and only with those who agreed will be contacted. Purposive sampling will be used to achieve variation in demographic characteristics which may include age, gender, ethnicity, and region. We anticipate a sample of around 12–15 participants should hold sufficient information power to meet the study objectives. A researcher will telephone the participant to conduct an audio-recorded interview, lasting up to 60 min, covering their reactions to the behavioural support programme and their views of the impact of the programme on their diabetes and wider health beliefs. The interviews will also explore in more depth, preliminary themes generated during pilot qualitative data collection and PPI focus group work, including: motivation for participation and health behaviour change in this population; perceptions of "success" and "failure"; and unintended consequences of engagement with the programme. We will analyse the data following a reflexive thematic analysis approach [25].

2.11. Retention and withdrawal

We will seek to follow-up all participants except those who expressly withdraw from the study. Participants who decide to withdraw from or discontinue the intervention allocated as part of the study will be asked to return for follow-up visits to collect outcome measures. We will seek consent from all participants to obtain data from medical records and use this to supplement missing data. To promote participant retention, participants will be offered a £20 gift card for attending the follow-up visits.

2.12. Adverse events

We will record adverse events (AEs) following Good Clinical Practice. We will ask nurses in the intervention arm to record adverse events of special concern; 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. At 12 months, we will record SAEs from the medical records for all patients; 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 our analysis, we will classify SAEs as diabetes-related (macrovascular or microvascular disease) or other. We will not prospectively record SAEs because this treatment is known to reduce the incidence of serious disease, and our retrospective recording will suffice to add to data on this.

2.13. Outcomes

The primary outcome is the difference in the proportion of patients achieving diabetes remission at 1 year from baseline, defined as off medication between 6 and 12 months and HbA1c $<$ 48 mmol/mol at 12 months.

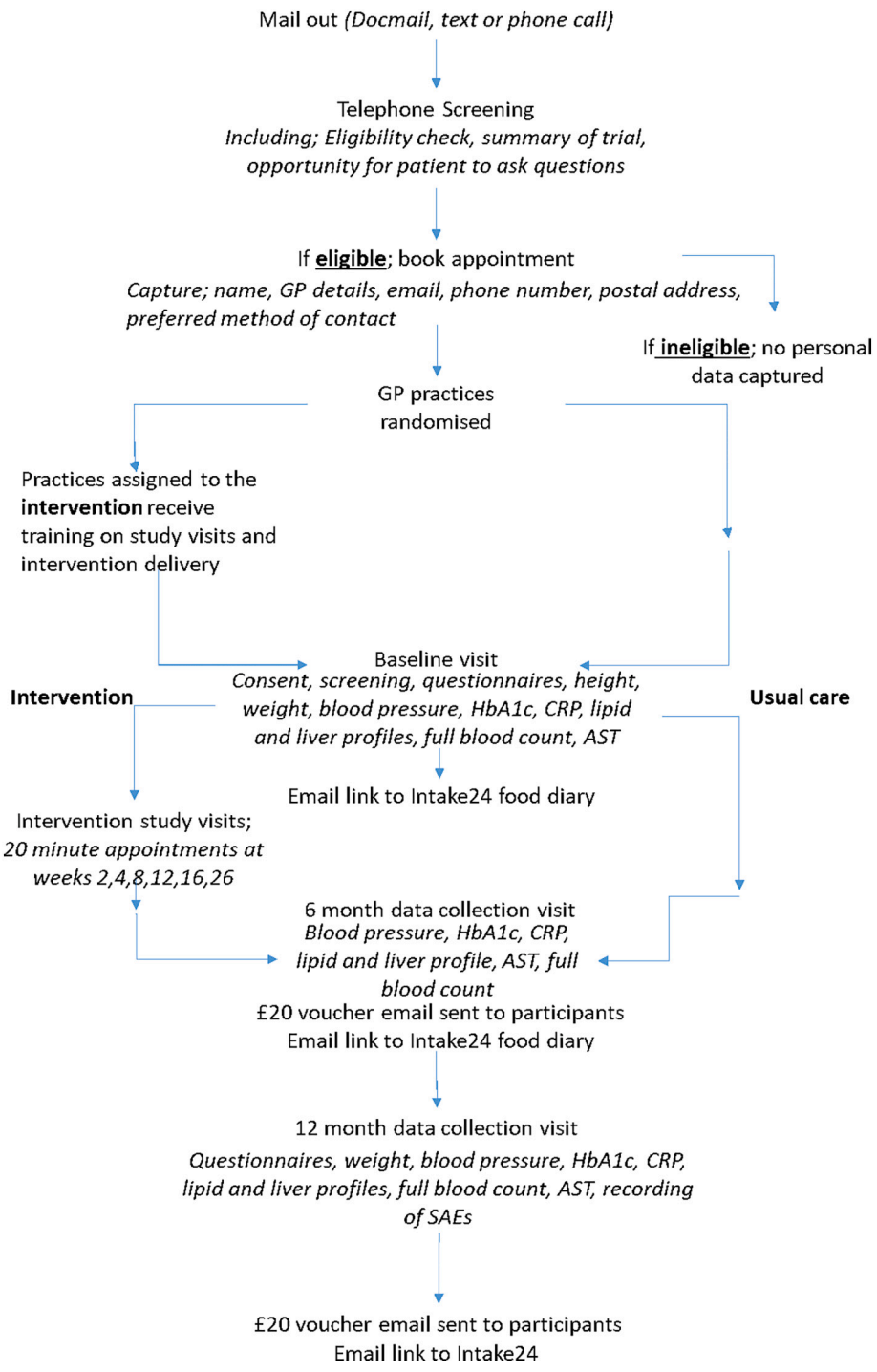

Fig. 1. Patient Flow.

2.14. Secondary outcomes

To assess the impact of the intervention on the following, between baseline and 12 months:

- Glycaemic control; concentration in HbA1c
- Lipid profile; total cholesterol/HDL ratio
- Blood pressure; systolic and diastolic blood pressure
- Cardiovascular risk; QRISK2 or SMART score
- Wellbeing; WHO-5 measure of wellbeing
- Diabetes distress; PAID

We will look at the cost effectiveness over the lifetime and return on investment in the short-term.

2.15. Exploratory outcomes

We will compare the effect of the intervention on the risk of liver fibrosis using the Fib-4 score. We will also assess the impact of the programme by age, gender, socioeconomic status, ethnicity, diabetes duration and number of diabetes medications used at baseline.

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	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	x	
24 hour dietary recall		x	x	x	
SAEs				x	
Intervention visits (intervention group only)			*		
Intervention group questionnaire (intervention group only)			*		
NHS Digital patient notes					x

Fig. 2. Schedule of measurements.

2.16. Process measures

We will compare the effect of the intervention on diet quality and weight. We will assess the impact of the programme on the participants' lives and behaviours, through interviews conducted up to three times throughout the intervention period.

2.16.1. Sample size

We assume 4% of control group participants will be in remission at 1-year, as in DiRECT [5], and that an increase to 15% would represent a valuable outcome to patients. With 95% 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 approximately 56 practices.

For the secondary outcomes, 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 [5,26].
 # power could not be estimated for the proposed sample size and given parameters.

To assess the acceptability of the intervention and inform future developments we will invite participants to take part in interviews until we reach sufficient information power. We estimate that a sample of approximately 15 participants (up to 3 interviews each) will be sufficient to meet the study objectives [27].

2.17. Randomisation

We will allocate practices to deliver either the DIAMOND programme or usual care using minimisation based on deprivation and ethnicity. Practices will be allocated after participants have been booked for the initial visit to prevent selection bias.

We will create three strata to define deprivation and two to define ethnicity. The strata are based on IMD deciles [1–10] and halves of the % non-white British (0–8.9, ≥9.0). Using Sortition (an online randomisation system developed by the University of Oxford Primary Care Clinical Trials Unit), 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 at cluster-level and concealed using Sortition.

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 trial team will inform the practice of this and proceed with staff training on the DIAMOND programme or continue usual care as appropriate.

2.18. Statistical analysis

We will analyse the outcomes using a three-level mixed-effects generalised linear regression model with appropriate link functions for binary data (logit or log) and continuous data using an identity link function. The models, where appropriate, will include data measured at

repeated time points, adjusting for minimization factors (ethnicity, socioeconomic status) and baseline measures. Practices will be included as a random effect as well as each participant, to account for the repeated measures on the same participant. A treatment-by-time interaction will be included to allow the treatment effect to differ at each time point. The model will allow for differing standard deviations 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. 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 [28,29]. For outcomes beyond one year, we will use mixed effects models to allow repeated measures at variable times as these outcomes are measured at routine reviews for people with diabetes, whether in remission or not.

2.18.1. Health economic analysis

We will use the NIHR School for Public Health Research (SPHR) Diabetes Prevention Model [30,31] to estimate the impact of diabetes remission, cardiovascular incidence, and complications of diabetes and impact on length and quality of life and the NHS costs compared with usual care. We will examine equity impact of this programme and cost-effectiveness in population subgroups (detailed methods described in supplementary appendix 2).

2.19. Data management

Data will be recorded in a web-based data capture system (REDCap), hosted by the Primary Care Clinical Trials Unit of the University of Oxford. This system is customised and has an audit trail facility. Validation checks are implemented in the system to aid reliable data entry.

2.20. Trial steering committee (TSC)

An independentTSC will provide oversight of all matters relating to participant safety, data quality and value to the public and includes two independent clinicians, statistician and two patient representatives. The TSC reviewed the protocol, statistical analysis plan and the suitability of the safety data to be collected. The TSC will decide on progression from the internal pilot at 4 months (supplemental table 1 for criteria).

2.21. Ethics and dissemination

The protocol (V1.1, 24th August 2022) was reviewed and approved by the East Midlands Nottingham 2 REC Committee (Ref: 22/EM/0074). Protocol modifications will be reviewed by the ethics committee and amended at the trial registry. Results will be disseminated publicly and to academic and health professional audiences at conferences and publication in peer-reviewed journals. If the intervention is shown to be effective, the results will be communicated to policymakers and commissioners of weight management services through briefing papers summarising the main findings. Results will be provided to all participants coincident with publication.

3. Conclusion

Remission from type 2 diabetes has always been seen as a theoretical possibility but rarely as a practical goal in the treatment of T2D. The DiRECT trial results changed that, and there is a new focus on achieving remission. Based on these data and other data showing the practicality of TDR in primary care [5,26], the NHS in England is rolling out diabetes remission services. Currently, only one option is available and people who do not want to pursue a TDR have no support to achieve remission. The aim of the DIAMOND is to provide another option. However, the aim of treating T2D is primarily to reduce the incidence of cardiovascular disease. We are therefore assessing cardiovascular risk factors and overall risk as key outcomes in this trial. The DIAMOND study will evaluate the long-term outcomes through linking with patient medical records and also assess cost effectiveness of the intervention, to facilitate the decision about whether to adopt the DIAMOND programme into health systems if it is effective. The results of the DIAMOND trial will be available from 2025.

Contributors

EM, SAJ and PA designed the study and secured the funding. All authors developed the protocol. EM, PD, JS, MN, DJ, GDT, RF, SAJ and PA developed the intervention. UG and LY are the trial statisticians.

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Declaration of Competing Interest

JS was involved with a Nestle Health Sciences advisory board and was an invited speaker at a Nestle Health Sciences webinar, for which a personal honorarium was received. GDT has attended conferences funded by Novo Nordisk. None of these activities led to personal payments. PAD was a member of the SACN sub-committee for low carbohydrate diets and T2D. PA and SAJ are investigators on a publicly funded trial where Nestle donated total diet replacement products to support the trial.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107199.

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