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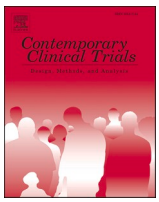

The impact of low-energy total diet replacement with behavioural support for remission of type 2 diabetes on disordered eating (ARIADNE): Protocol for a non-inferiority randomised controlled trial

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ABSTRACT

Introduction: The National Health Service (NHS) in England is currently piloting a weight loss programme for remission of newly diagnosed type 2 diabetes (T2D), where participants replace all food with low-energy nutritionally complete formula products for 12 weeks (total diet replacement, TDR) and receive behavioural support. In a clinical trial, this programme led to remission in nearly half the participants. However, this weight loss programme might also worsen disordered eating and prompt eating disorders in susceptible people. We aim to investigate if the TDR programme is non-inferior to standard care in terms of disordered eating in susceptible individuals.

Methods: Fifty six people with newly diagnosed T2D, BMI $\geq$ 27 kg/m^2, and medium to high scores of disordered eating based on the Eating Disorders Examination questionnaire (EDE-Q) will be randomised 1:1 to TDR receiving remote weekly/bi-weekly dietetic support or standard care. Participants will be re-assessed remotely at 1, 3, 4, 6, and 12 months. The primary outcome will be the between-group difference in the score of the EDE-Q. If the sample size can be expanded to 150, we will reduce the non-inferiority boundary. Weight, glycated haemoglobin (HbA1c), impairment from disordered eating, and distress will be secondary outcomes. Using the recorded consultations, we will evaluate the process in observed changes in eating behaviour and disordered eating.

Conclusions: If TDR for T2D remission is deemed non-inferior to standard care, more people may enrol and benefit from T2D remission. If TDR exacerbates disordered eating, screening may reduce unintended harm.

Trial Registration: NCT05744232 (ClinicalTrials.gov, prospectively registered).

1. Background and rationale

Type 2 diabetes (T2D) is one of the most common non-communicable diseases globally, with 437.9 million prevalent cases in 2019 [1]. >4 million people live with T2D in the UK alone [2]. T2D is routinely managed with dietary modification and medication. However, achieving disease remission is the top priority for patients, clinicians, and policymakers [3], because it improves quality of life, prevents morbidity [4], and reduces healthcare costs [5]. A known mediator of disease remission is substantial weight loss [6]. The Diabetes Remission Clinical trial (DiRECT) showed that a low-energy total diet replacement (TDR) programme with behavioural support leads to an average 10 kg weight loss at 1 year and induces T2D remission in 46% of patients [7]. Based on this and another trial [8], the NHS in England is piloting TDR programmes for T2D remission in 10,000 patients [9]. If the pilot is successful, it is likely that TDRs will be adopted as standard treatment in routine care. However, a caveat exists.

Despite their promising pathophysiological benefits, TDRs are a form of rigid dieting, encouraging participants towards restraint and a focus on self-monitoring of weight and dietary intake. These are features of disordered eating and eating disorders [10,11]. Dieting, following specific eating rules resulting in limited dietary intake may lead to physiological and a psychological sense of deprivation [12]. In early starvation studies, people were found to be pre-occupied with food and

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eventually overconsume food, despite abundancy [13,14]. In people with eating disorders, opportunities to override these rules sometimes prompt rule-breaking, creating a sense of failure that results in overeating with loss of control (bingeing), followed by renewed restraint, lowered self-esteem, and this progresses to a vicious circle. Therefore, there are concerns that TDRs, by advising total abstinence from regular food for 12 weeks, may lead to disordered eating in susceptible people or significantly worsen existing symptoms. Eating disorder charities have expressed concerns and suggested screening before referring; however the pilot continues to expand without screening at this stage in the absence of evidence of harm. Furthermore, healthcare professionals have previously offered TDRs only to 7% of patients, being hesitant due to safety fears about the potential negative psychological impact [15], as disordered eating is associated with lower quality of life [16], and higher morbidity and mortality [17]. These concerns need to be addressed before wider adoption of TDRs in routine care.

It is also important to distinguish between disordered eating and eating disorders. Eating disorders are diagnosed clinically based on an interview and observation [18], whereas disordered eating, is defined here as the sub-clinical condition where people experience suboptimal relationship with their body image and eating, but impairment is not enough to justify a diagnosis of an eating disorder. Disordered eating is estimated to affect up to 20% of people with overweight and T2D [19]. The evidence is sparse on the effect of TDRs on eating behaviour. A systematic review on the effect of severe energy restriction on binge eating post intervention in populations with either no disordered eating, sub-clinical disordered eating or diagnosed binge eating found 10 trials (5 with pre-post designs) of diet replacement programmes [20]. The evidence was limited and the direction of effect varied and seemed to relate to whether people had subclinical binge eating disorder at baseline. Among people with clinical binge eating disorder at baseline, severe energy restriction seemed to be associated with reduced binge eating but the direction of effect was less clear among people without binge eating or with subclinical binge eating at baseline. In uncontrolled studies, this could represent regression to the mean. Another systematic review showed no evidence that weight management programmes increased eating disorder symptoms for most adults, except a subgroup of people who might develop disordered eating symptoms [21].

There are also substantial differences between self-directed rigid dieting and structured TDR. Compared with self-directed rigid and severe energy restriction typically preceding eating disorders, formal TDRs include significantly more support and dietary regimes of higher nutritional quality during the food re-introduction phase [22]. This is an important distinction, because the period of re-introduction of regular food after TDR could be critical for the onset of disordered eating symptoms, as it can be less straight-forward for patients compared to the TDR phase, due to fear of regaining weight loss [23]. These factors may mitigate the risk of worsening of symptoms during or after TDR [20]. Achieving larger weight loss after formal weight loss programmes is associated with less binge eating [24] and bariatric surgery is also associated with clinically significant reductions in disordered eating [25]. TDRs achieve larger mean weight loss than standard weight loss programmes, so it is plausible that even if they do not improve disordered eating, they would at least not worsen it. In such a scenario, they could be recommended for remission of T2D to everybody eligible, so that all patients can benefit. If on the other hand, they are harmful, appropriate screening is needed to exclude people for whom it may cause harm. A non-inferiority randomised controlled trial (RCT) is needed to examine this hypothesis.

2. Objectives

Primary objective: To investigate if TDR is non-inferior to standard care in terms of disordered eating in people with T2D and disordered eating in people aiming to achieve diabetes remission through a TDR programme. We will assess between-group changes in the symptoms of disordered eating using the global EDE-Q score with a non-inferiority margin of one standard deviation at 6 months in the first instance.

Secondary objectives:

- To investigate if TDR is non-inferior to standard care for changes in sub-scale scores of disordered eating by measuring the between-group changes in the subscale scores of EDE-Q (restraint, eating concern, shape concern, weight concern).
- To investigate if TDR is non-inferior to standard care for changes in psychosocial impairment by measuring the between-group changes in the self-administered clinical impairment assessment (CIA) questionnaire scores.

Exploratory objectives:

1. To explore the changes in medication (self-reported by participants) between TDR and control.
2. To explore the changes in quality of life between TDR and control.
3. To evaluate the process of change, by attempting to understand experiences, barriers, facilitators, and changes in eating behaviour and disordered eating symptoms, using qualitative analysis.
4. To examine the safety signals of TDR in people with disordered eating, by determining the incidence of cases of high suspicion of a new eating disorder, measured by referral of the participant to see their general practitioner (GP) for possible referral to specialist services. This will be assessed by the clinician delivering the intervention, who will discuss cases with the supervisory team and the data monitoring and ethics committee (DMEC).

2.1. Trial design

Non-inferiority, individually randomised controlled trial.

3. Methods

3.1. Study setting

ARIADNE aims to recruit 56 participants initially across England through digital means, aiming to achieve diversity of the population by geographical location and deprivation.

3.2. Eligibility

The study aims to recruit participants residing in England with a T2D diagnosis in the last 6 years, overweight/obesity and disordered eating. Table 1 presents the key inclusion/exclusion criteria. The study aims to be pragmatic, offering insight for the safe implementation of the NHS T2D Path to Remission Programme. As a result, the eligibility criteria mirror the enrolment criteria for the NHS T2D Path to Remission Programme with the addition of criteria for disordered eating [26]. We defined a score $\geq$ 2.67 as indicating disordered eating, as proposed by Mond and colleagues in 2008 [27] for an "older" population, given the risk of T2D increases with age [28]. In addition, people living with overweight/obesity tend to score higher than people with a BMI <25 kg/m^2. Indeed, a Norwegian study showed that obesity (BMI $\geq$ 30 kg/m^2) was associated with 2.3 times greater global EDE-Q score [29]. Newly diagnosed diabetes is defined by the NHS T2D Path to Remission Programme as diagnosed in the last 6 years and it has been adopted by the DiRECT study [30]. People with a suspected and/or diagnosed eating disorder will be excluded from the programme, following existing NHS guidelines and by excluding anyone with a combination of an EDE-Q $\geq$ 4 and clinical impairment assessment (CIA) score $\geq$ 16, as this might indicate an undiagnosed eating disorder.

Interested potential participants will be asked to read the participant information sheet and complete the eligibility assessments online. A

Table 1
Key inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Willing and able to give informed consent and can communicate in English	Self-reported current or previous clinical diagnosis of an eating disorder
Age 18–65 years	Combination of EDE-Q ≥ 4 AND a clinical impairment assessment (CIA) score ≥ 16 at screening
Resident in England	Currently participating in a structured weight loss programme or self-reporting weight loss of >10% in the last 3 months
BMI ≥27 kg/m2 (≥25 kg/m2 for people of Black, Asian and minority ethnic origin)	Insulin use
Diagnosed with T2D within 6 years prior to the day of screening	Known kidney disease of stage 3/4/5 or eGFR <60 mls/min/1.73 m2 within the last 12 months
Global EDE-Q scores ≥2.67	Active substance use disorder
HbA1c ≥43 mmol/mol (6.1%) and ≤ 87 mmol/mol (10%) if on diabetes medication OR latest hbA1c ≥ 48 mmol/mol (6.5%) and ≤ 87 mmol/mol (10%), if not on diabetes medication, done within the last 12 months	Porphyria or active liver disease (not including non-alcoholic fatty liver disease)
	Known proliferative retinopathy that has not been treated
	Undergone or awaiting bariatric surgery
	Myocardial infarction or stroke within the previous 6 months
	Severe heart failure (New York Heart Association grade 3 or 4)
	Pregnant, breastfeeding, or planning to become pregnant during the course of the study
	Soy or fish or milk allergy, lactose intolerance, or following a vegan diet
	Active cancer other than skin cancer

member of the study team will confirm eligibility over the phone. Where this assessment raises concerns about eligibility, we will discuss this with the potential participant's GP to assess if the programme would be safe clinically. If eligible participants are following any other diet, they will have to agree to follow the TDR programme, if randomised to intervention.

3.3. Intervention

Participants in this group receive behavioural support 1:1 with a dietitian over the phone over 6 months, similar to the NHS T2D Path to Remission Programme [9]. Once randomised to intervention, participants book their first appointment with the study dietitian and receive the intervention booklets and meal replacement products by post, along with blood pressure monitor, blood glucose monitor and a weighing scale, if they don't have one.

The first stage (Week 1–12) is low-energy total diet replacement in a nutritionally replete package of soups, shakes, and bars (4 per day providing ~850 kcal/day) provided at no cost to participants. The study GP reviews their medication and advises on appropriate changes for T2D and hypertension medication. The study GP will stop all medications for diabetes in people on two or fewer medications and stop two medications in people on three or more and continue only on one medication that poses no risk of hypoglycaemia or ketoacidosis, according to standardised guidance [31]. The intervention continues with stepped food reintroduction (Week 12–20) where participants gradually decrease the number of meal replacement products and increase regular meals, aiming for participants to eat an energy-restricted and nutrient-rich diet personalised to the participant's circumstances and preferences. The final stage is weight maintenance (~2 weeks) when participants return to eating only regular food. Participants have sessions with the study dietitian weekly or bi-weekly, depending on the stage and amount of support they require. Typically, participants receive 12 sessions over 6 months lasting 10 to 40 min, depending on the stage and amount of support needed. Behaviour change techniques include motivational interviewing, problem solving, exploring social support, and goal setting. Participants are advised to self-monitor their blood glucose and blood pressure twice a week (or more often if required) throughout the programme and report this to the dietitian who will pass to the GP to change medication if hyper/hypoglycaemia and hyper/hypotension occur. Adherence to the programme is monitored by self-report and weight loss (with non-adherence defined as weight loss of <5% at 6 months compared to baseline). The details of the programme can be found in Table 2. We will report the number of people receiving more than the pre-specified number of support calls and the number of the additional calls they received.

3.4. Care as usual group

The standard of care group are not given specific advice on diet or self-monitoring. As this is a non-inferiority trial, the comparator is standard care, as offered by the participant's GP. This can vary depending on the area and time since diagnosis. According to National Institute for Health Care Excellence [32], patients with T2D should be offered a structured education programme at diagnosis, with annual reinforcement and reviews. For people living with T2D, the recommendations focus on lifestyle changes including diet and exercise, with or without medication. First line medication is usually metformin, and depending on how well blood glucose is controlled, medication might be up titrated in dose and/or additional agents.

3.5. Outcomes

3.5.1. Primary outcome

Change in the global score of the self-administered EDE-Q measured at 6 months.

The EDE-Q [33] is used to measure disordered eating. EDE-Q is a 28-item self-report questionnaire that measures the frequency and severity of thoughts, emotions, and behaviours characteristic of the psychopathology of disordered eating. It consists of four subscales; restraint, eating concern, shape concern, and weight concern. Scores are calculated for each subscale and added to create a global score. It was developed based on the Eating Disorder Examination Interview (EDE-I), which is considered the gold standard in disordered eating assessment, and hence selected as the primary outcome. EDE-Q has demonstrated good level of agreement to EDE-I when used in the general population [34] and clinical populations [35]. Two versions of the questionnaire will be used; the full one to assess the outcome and the "amended" version to assess safety throughout the study (see **Appendix 1.)** We amended this to remove items that would necessarily change if participants adhered to the TDR programme- for example participants are asked about excluding particular foods, which participants on a TDR must do. Leaving these in would have led to spurious increases in one arm and mask true changes in psychopathology that might arise.

3.5.2. Secondary outcomes

Change in the subscale scores of EDE-Q (restraint, eating concern, shape concern, weight concern) measured at 6 months.

Change in psychosocial impairment, using between-group changes in the self-administered CIA questionnaire scores measured at 6 months.

The CIA score [36] measures the severity of psychosocial impairment associated with disordered eating. It is a 16-item self-report measure that assesses functional impairment from disordered eating in various domains of life and complements the EDE-Q questionnaire scores.

Change in self-measured weight between TDR and control at 3, 6 and 12 months.

Weight is self-reported with a home measurement. Participants

Table 2
Intervention timetable and content.

	Formula Products	Breakfast	Lunch	Dinner	Fruit	Appointment details
Weeks 1–12 Total Diet replacement (~850 kcal)	4×	-	-	-	-	Weekly/ Fortnightly 15–45′
Weeks 13–14 Food reintroduction I (~850 kcal)	3×	-	-	200 kcal + veg	1×	Weekly 15–30′
Weeks 15–16 Food reintroduction II (~1000 kcal)	2×	-	200 kcal + veg	400 kcal + veg	2×	Fortnightly 15–45′
Weeks 17–20 Food reintroduction III (~1200 kcal)	1×	200 kcal	200 kcal + veg	400 kcal + veg	2×	Fortnightly 15–45′
Weeks 21–24 Maintenance (Personalised healthy balanced diet)	-					Weekly/ Fortnightly 15–30′

receive instructions on measuring their weight in a standardised manner (e.g., light clothing, same day of the week, early morning, fasted).

3.5.3. Exploratory outcomes

Change in the number of diabetes medications between baseline and 3, 6, and 12 months.

Change in diabetes distress and depression between TDR and control, measured by the PAID and PHQ-9 questionnaires, at 3, 6 and 12 months.

The Problem Areas in Diabetes score (PAID) [37], a 20-item self-administered questionnaire, measures diabetes distress. The Patient Health questionnaire (PHQ-9) [38], a 9-item self-administered questionnaire that measures symptoms of depression. If a participant scores highly on reporting "Having thoughts that you would be better off dead or of hurting yourself in some way", the questionnaire will be shared with the participant's GP.

3.6. Process evaluation

Experiences, barriers, facilitators, and changes in eating behaviour and disordered eating symptoms, by conducting qualitative analysis of the transcribed sessions with the dietitian throughout the intervention.

We aim to assess changes in disordered eating in participants in the intervention and control groups. For participants in the intervention group, we will analyse intervention sessions from 20 purposively selected participants. We are recording all intervention sessions and will choose participants who experience a change in their scores of at least 1 standard deviation (SD) and others who continue within this bound, and participants whose scores rise above the clinical cut-off of 4. During the intervention sessions, participants typically discuss their experience, barriers, facilitators, and changes in eating behaviour and disordered eating symptoms. Secondly, at 12 months, all intervention participants will be asked to rate the programme by responding to a 5-point Likert scale question: "Overall, I am satisfied with my experience of the programme", and will be asked to explain their reasoning beneath and we will analyse all these responses. Thirdly, we will ask a purposive sample of participants from the intervention and control groups to take part in a reflective interview, again selecting participants for this based on change in EDE-Q scores. The focus of these interviews will be on the change in scores and psychopathology of disordered eating. Data will be analysed in NVivo using content analysis [39]. A second coder will code a 10% subsample of the data and inter-rater reliability will be assessed.

The scope and size of the process evaluation is limited by resources available to complete the study, but we expect that the sample will be sufficient to elucidate reasons behind any change in EDE-Q scores that we see.

3.6.1. Safety objective

This will be measured by referral of participant to see their GP for further referral to specialist services throughout the programme. This will be decided by the study dietitian delivering the intervention when there are concerns voiced by participants signifying disordered eating, along with disordered eating scores (EDE-Q) and its impairment (CIA) increasing above cut-offs of 4 and 16 respectively [34], after discussing with supervisory team and/or the study DMEC.

3.6.2. Participant timeline

Schedule of study procedures is presented in Table 3. (See Table 4.)

3.6.3. Sample size

If the maximum change allowed for non-inferiority would be a change of EDE-Q global score equivalent to 1 SD from the population mean, then 44 people ($n = 26$ per group) are needed to be 95% sure that the upper limit of a 90% two-sided confidence interval will be below the non-inferiority limit of +1SD. One SD was derived as the minimum clinically meaningful change based on feedback from clinicians, academics, and a statistician. Accounting for a 25% dropout, 56 participants ($n = 28$ per group) are needed.

3.6.3.1. Scope for expansion of sample size. In discussions with policy stakeholders, we have secured additional resources to expand recruitment. If the recruitment to the expanded study is successful, we will impose a stricter non-inferiority margin 0.5 SD, which will give greater confidence that the programme is not harmful or may be harmful. A non-inferiority margin of 0.5 SD will need 138 people ($n = 69$ per group) to be 90% sure that the upper limit of a 90% two-sided (or 95% one-sided) confidence interval will be below the non-inferiority limit of 0.5 SD. Accounting for a 10% dropout, 154 participants ($n = 77$ per group) would be needed., The expansion of the trial has received ethical approval by NHS ethical review.

3.6.4. Recruitment

To identify potential participants, we will (a) place adverts on the online forum of the Diabetes UK charity and (b) utilise a digital marketing recruitment service (Health Research https://www.healthresearch.study/) which will show ads on popular websites (e.g. Google, Facebook) to potentially eligible participants. If people living with T2D find out about their study through existing trial participants, they could self-refer to the trial by contacting the study team.

3.7. Assignment of intervention, randomisation and blinding

Following eligibility confirmation and the baseline assessment, participants are randomised to one of the two study arms using a minimisation software (MinimPy [40],) with a 20% random element balancing gender (man/non-binary/other or woman) and EDE-Q global score ($\geq$3.9 and $<$ 3.9). The 3.9 cut-off for EDE-Q was chosen based on previously reported means of EDE-Q scores on populations with obesity and subclinical disordered eating [41,42]. Randomisation is conducted by a researcher (DAK) blinded to baseline data who is then informs the lead researcher (ET). ET then informs the participant about their allocation. Due to the nature of the intervention, it is not possible to blind neither participants nor clinicians delivering the intervention. However,

Table 3
Schedule of study procedures.

	Week − 2	Week 0	1 month (±1 week)	3 months (±2 weeks)	4 months (±2 weeks)	6 months (±3 weeks)	12 months (±4 weeks)
	Screening / Baseline		Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5
Posting scales	x						
Confirming with GP if eligible	x						
Informed consent	x						
Demographics	X*						
Diabetes history	X*						
Concomitant medication	X*			x		x	x
Self-weighing		x*	x#	x	x#	x	x
Self-reported height	X*						
EDE-Q, CIA	X*		x	x	x	x	x
PAID, PhQ-9	X*			x		x	x
HbA1c home kit						x#	
Adverse event assessments			x	x	x	x	x

* Data retained only if eligible, #only for participants in the intervention arm.

Table 4
Sample size calculations.

Non-inferiority limit, d	SD of outcome	Study derived	Significance level (α)	Power (1-β)	Sample size (n per group)	Sample size after % attrition
0.97	0.97	Aardoom et al., 2012 [42]	5%	95%	44 ($n = 22$)	50 ($n = 25$), 14%
1SD (e.g. 0.97)	1 SD (e.g. 0.97)	Aardoom et al., 2012 [42]	5%	95%	44 (n = 22)	56 ($n = 28$), 25%
½ SD (0.485)	1 SD (0.97)	Aardoom et al., 2012 [42]	5%	90%	138 ($n = 69$)	154 ($n = 77$), 10%
½ SD (0.485)	1 SD (0.97)	Aardoom et al., 2012 [42]	5%	95%	174 ($n = 87$)	192 ($n = 96$), 10%
½ SD (0.485)	1 SD (0.97)	Aardoom et al., 2012 [42]	5%	95%	174 (n = 87)	218 ($n = 109$)

the assessment of the primary outcome will be blinded, as questionnaires are self-administered online.

3.8. Data management

Data will be recorded directly onto the case report form (CRF) by participants into REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Oxford on a secure server [43]. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The system has an inbuilt audit trail facility and ability to run internal validation checks. Entries are embedded with mandatory fields are required and range checks in order to minimise the risk of missing data and data queries. The study will comply with the UK's General Data Protection Regulation (UK GDPR) and Data Protection Act 2018 so, at the end of the study, de-identified data will be transferred to a database for analysis.

3.9. Statistical analysis

Participant flow will be recorded and reported in accordance with the CONSORT 2010 guidelines. Regarding the non-inferiority limit, it has been set to 1 SD for both the primary outcome (EDE-Q) and the two secondary outcomes (all EDE-Q subscales and CIA). The reference SD will be the pooled baseline standard deviation of all the eligible participants interested in the study, regardless of whether or not they were randomised.

Descriptive statistics of recruitment, drop-out, and adherence to intervention will be reported. The intention-to-treat population will be used for the primary analysis regardless of group allocation or intervention adherence. Each continuous endpoint will be assessed with a linear mixed-effects model with repeated measures adjusting for treatment group, timepoint, and baseline minimisation factors as fixed factors and participant as a random effect. The treatment effect will be given by including a timepoint X treatment group interaction term. Categorical variables will be modelled with an analogous generalised linear mixed effect model.

Missing data will be handled through the mixed-effects model, which assumes data are missing at random. Investigating the reasons behind missingness of different data will also help interpret the results appropriately. We will perform Kendall's tau-b and Wilcoxon's test if data are not amenable to regression analysis.

To assess the robustness of the non-inferiority conclusion, we will also analyse in a secondary analysis the per-protocol population (according to adherence) [44], including intervention participants who have achieved at least 5% weight loss at 6 months, and excluding participants in the control arm who follow a TDR programme at any time during the first 6 months. We will also conduct sensitivity analysis with a two-sided 95% confidence interval to assess superiority, and analyse the primary outcome using the complete questionnaire score. Exploratory analysis will be conducted to assess whether there is evidence that effects depend upon participants age, gender, or socioeconomic status, identify characteristics of patients whose scores changed more than the non-inferiority margin and in participants deemed non-adherent (<5% weight loss).

3.10. Monitoring

The Data Monitoring and Ethics Committee consists of a chair who is an academic clinician in eating disorders, an expert in obesity, and a statistician with experience in the field, all independent of the sponsor with no competing interests. The committee will receive and review the progress and accruing data of this trial. The committee's role is to safeguard the interests of trial participants, assess the safety of the interventions during the trial, to ensure continued trial integrity, scientific value, and ethical treatment of study subjects and monitor the overall conduct of the trial. The committee will meet with the trial management every 6 months or whenever deemed necessary.

Adverse events related to physical health in people following the TDR programme have been extensively assessed and reported in previous studies. One previous trial reported no SAEs due to the TDR, whereas another reported two SAEs potentially related to the TDR intervention in the same participant [7,8]. There has been evidence that for every five

people in the TDR intervention, one would experience an adverse, mostly mild, event [7]. The most common AEs reported are constipation, headache, fatigue, and dizziness; they however occurred in a minority of participants (<8% each) and disappeared over time in previous studies [7,8]. Therefore, only serious or severe (but not mild or moderate) adverse events will be monitored in this study reducing the participant burden.

3.11. Research ethics and protocol amendments

This study has received ethical approval from the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) of the University of Oxford (for the first 56 participants) and expansion of recruitment will be attempted (154 participants), with ethical approval received from the Camberwell and St Giles NHS Research Ethics Committee. Protocol amendments will be implemented only following notification and/or approval by the relevant ethics committee, and they will be communicated to the trial registry and outlined in publications.

3.12. Patient involvement

We consulted individuals living with obesity and T2D throughout the development of the trial; from conceptualising the research idea and applying for funding to writing the protocol and applying for the study's ethical approval. We will continue consulting with lay members to effectively communicate the results of this study.

3.13. Dissemination

This work will form ET's DPhil thesis. The protocol and results will be published in open access journals and will be presented in conferences nationally and internationally. Publication of results will not depend on the findings. A summary of results will be disseminated to the study participants, Diabetes UK, and other relevant patient charities. Briefs will be also disseminated to NHS England and local diabetes services.

4. Discussion

This will be the first study, to our knowledge, to explore the impact of a TDR intervention similar to the NHS Type 2 Diabetes Path to Remission Programme on disordered eating in susceptible individuals. This study addresses concerns voiced by eating disorder charities, healthcare professionals, and patients around the programme which is currently piloted with the intention to be offered to everybody with T2D and overweight/obesity in England. If the study shows that the programme is significantly increasing scores for disordered eating compared to standard care, implementation of screening can be considered. If the study shows that this is not the case, then this can provide reassurance to relevant stakeholders.

This study has some strengths; it is the first to determine the impact of TDR programme for diabetes remission on disordered eating in susceptible people and therefore may shape policy for the benefit of patients and healthcare practice. Adding the qualitative element may help elucidate why the EDE-Q scores change and the role of the weight loss programme in those changes. A key limitation is that we are using a questionnaire to assess eating disorder psychopathology, meaning that we cannot assess whether participants have or develop an eating disorder.

Author contributors

ET, DAK, PA, RJP developed the concept and designed the study. ET is responsible for data management. ET drafted the manuscript for publication, with input from DAK, PA, RJP. All authors approved the final manuscript.

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Ethical approval

The study protocol (version 1.1, R82152/RE002) was reviewed and approved by the Medical Sciences Interdivisional Research Ethics committee (CUREC 3) and the Camberwell and St Giles Research ethics committee (REC reference: 23/LO/0633).

Patient consent statement

All participants will provide written informed consent online.

Independent data monitoring and ethics committee

Professor Zafra Cooper, Professor Louisa Ells, Mr. Dominic Stringer.
Trial management committee: ET, PA, DAK, RP.
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Roles and responsibilities: ET, DAK, RJB, PA conceived the study and initiated the study design. DAK and PA provided statistical expertise in the clinical trial design. ET is the grant holder. All authors contributed to refinement of the study protocol and approved the final manuscript.

CRediT authorship contribution statement

E. Tsompanaki: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. **P. Aveyard:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **R.J. Park:** Conceptualization, Supervision, Writing – review & editing. **D.A. Koutoukidis:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ET has been awarded the Doctoral Fellowship in Clinical Diabetes 2021 by the Novo Nordisk UK Research Foundation, member of the Association of Medical Research Charities. The funder had no involvement in designing and conducting this study.

DAK and PA are investigators in two investigator-led publicly funded (NIHR) trials where the weight loss intervention was donated by Nestle Health Sciences and Oviva to the University of Oxford outside the submitted work. None of these associations led to payments to these authors. No other conflicts of interest are reported.

Data availability

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

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Appendix A. Appendix 1

Amended versions of the questionnaires will be used to assess safety; the complete score as intended will be used for the outcomes, to ensure validity is maintained.

During the follow-up time points, participants will be asked to fill in the relevant questionnaires in full, however the following questions from the EDE-Q will be omitted from calculating the total average score at follow-ups ("amended" version):

- Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?
- Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?
- Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?

The following questions from the CIA questionnaire will be omitted as well from the analysis ("amended" version):

- To what extent have your eating habits/exercising/or your feelings about your eating/shape/weight interfered with meals with family or friends?
- To what extent have your eating habits/exercising/or your feelings about your eating/shape/weight made it difficult to eat out with others?

Appendix B. Appendix 2

Intervention in detail

1. **Weeks 1–12 (TDR phase)**: The first session will be around 45 min long and the rest of the sessions will be around 15–30 min long delivered over the phone. They will occur approximately at Week 0, 1, 2, 4, 6, 8, 10 and 12, but this can be modified according to participants' needs and the dietitian's judgement. Participants will be encouraged to consume 4 formula products offered for free by the study team. There will be an allowance of up to 100 ml of skimmed milk (for coffee, tea etc.), if needed. During the sessions at week 10 and 12, the dietitian will start discussing the food reintroduction phase.
2. **Weeks 13–14 (Food reintroduction phase I):** These weekly sessions will be approximately up to 30 min long. Participants will be advised to consume 3× formula products offered for free by the study team with an allowance of up to 100 ml of skimmed milk (for coffee, tea etc.), if they need it. They will be also advised to consume a small high-protein, low-carbohydrate, low-fat meal (approximately 200 kcal), unlimited salad/non-starchy vegetables and one portion of fruit.
3. **Weeks 15–16 (Food reintroduction phase II):** This single session will be 15–30 min. Participants will be advised to consume 2× formula products per day. They will be also advised to consume a lunch based on a small high-protein, low-carbohydrate, low-fat meal, unlimited non-starchy vegetables (e.g. made into a salad or soup), 2 portions of fruit, and ~ 400 kcal evening meal based on the healthy eating guidance.
4. **Weeks 17 till 20 (Food reintroduction phase III):** The sessions on weeks 17 and 19 will be 15–30 min long. Participants will be advised to consume one formula product, plus meals to continue weight loss or maintenance according to participant preference. At this stage, the dietitian will start discussing physical activity and some mild exercise will be recommended, according to what the participant used to do before the programme and is able to now incorporate into their day to day life.
5. **Weeks 21 till 24 (Maintenance phase):** The sessions on weeks 21, 23, and 24 will be 15–30 min long. Participants will be advised to consume regular food based on the healthy eating guidance in quantities to aid weight loss maintenance. There will be a provision for an optional small treat (up to 300 kcal) a week. The standard UK Chief Medical Officers' Guidelines on physical activity will be also discussed with the participant: at least 150 min moderate intensity activity, 75 min of vigorous activity, or a mixture of both, strengthening activities on two days and reducing extended periods of sitting.

In the end of the intervention, participants will be offered an HbA1c home test kit in order to safely hand them over to their usual care provider/GP. The result will help inform their new HbA1c baseline, if they have completed the programme successfully, or consider titrating/restarting medication if they have not adhered to the programme as well.

Behavioural content

Week(s)	Appointment name	Learning topics and key outcomes
0	Initial consultation	The Dietitian: • introduces themselves and gives an overview of the programme • collects participant history and current medications • assesses motivation and current lifestyle including diet, lifestyle and exercise • problem solves potential barriers • provides education for the TDR stage
1, 2, 4, 6, 8, and 10	Phase 1- Total Diet replacement	The Dietitian: • reviews weekly progress, including weight change and any issues with blood pressure and blood glucose, if applicable. • checks product tolerance and usage of fibre supplement • help participant problem solve any issues encountered • ensures ongoing self-monitoring and goal setting continues
12	Wrap-up of phase 1 Phase 2- Food reintroduction	The Dietitian: • covers progress summary to close the TDR phase reflecting, by asking questions like: -What went well? -What were the challenges? • reviews total weight loss, blood glucose and blood pressure review • reviews initial goals • explains the phase of food reintroduction • signpost to meal plan resources, cooking methods, and recipes • ensures ongoing self-monitoring and goal setting continues
13, 14	Phase 2- Food reintroduction	The Dietitian: • reviews weekly progress including weight change and any issues with blood pressure and blood glucose • works with each participant to create and maintain an individualised diet plan • looks at any deviations from dietary protocols and problem solve as required • helps problem-solve as required • ensures ongoing self-monitoring and goal setting continues
15, 17, 19,	Phase 2- Food reintroduction II, III	The Dietitian: • reviews progress undertaken including achievements, challenges, weight lost, changes in blood glucose or blood pressure • ensures ongoing self-monitoring and goal setting continues
20, 21, 23	Phase 3- Maintenance	The Dietitian: • closes the stage of food-reintroduction • assesses against participant's initial goals • offers guidance on the calculated calorie requirements for the maintenance phase • works with each participant to create and maintain a dietary pattern to sustain weight loss • reviews progress over previous month, help break down any issues/barriers/ lapses, using behavioural change strategies throughout • ensures ongoing self-monitoring and goal setting continues
24	End of programme	The Dietitian: • undertake progress review of the last 6 months including achievements, challenges, changes in dietary choices, portions and patterns • revisits initial and evolved goals and expectations • helps planning ahead with future goal setting and signpost to local services • ensures ongoing self-monitoring and goal setting continues

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