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Prevention Of Breast and Endometrial cancer using Total Diet Replacement (PROBE-TDR) trial: protocol for a randomised controlled trial

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ABSTRACT

Introduction Obesity and overweight are strong potentially modifiable risk factors for postmenopausal breast and endometrial cancer. Bariatric surgery can achieve considerable weight loss and risk reduction of weight-related cancer but is unlikely to be a feasible cancer prevention strategy. Total diet replacement (TDR) can also lead to significant weight reduction. This study aims to examine the cellular and molecular changes in breast and endometrial tissue in high-risk women following TDR-induced weight loss, as well as longer-term adherence to a 12-month TDR weight loss intervention.

Methods and analysis PROBE-TDR (PRevention Of Breast and Endometrial cancer using Total Diet Replacement) is a prospective, non-blinded, randomised controlled trial of 47 women at increased risk of breast and/or endometrial cancer. Randomisation is 2:1 to either an immediate 12-month TDR weight loss programme (n=31) or delayed dietary intervention (control) (n=16). The TDR programme includes an initial 12-week period of TDR (850 kcal/day) followed by a 40-week food-based diet, based on the nutritional principles of a Mediterranean diet, as either continued weight loss (~1500 kcal/day) or weight loss maintenance (~2000 kcal/day). Menstrual phase-matched biopsies of the breast and endometrium will be assessed at baseline and at the end of the 12-week TDR in the immediate diet group, compared with women randomised to the control group following their usual diet. The trial will also assess longer-term adherence and weight loss success across the 12-month programme in both the immediate and control groups.

Ethics and dissemination Approval for this study has been obtained from the Health Research Authority and Health and Care Research Wales (approval 20/NW/0095). Results will be published in peer-reviewed journals, presented at conferences and shared with trial participants.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ First study to evaluate the impact of diet-induced weight loss using total diet replacement in both breast and endometrial tissues, in high-risk women, with a two-stage design assessing tissue changes and longer-term adherence.
⇒ Provide proof of principle for weight loss and reduction in breast and endometrial cancer risk through biological measures and longer-term adherence.
⇒ Relatively small sample size may preclude adequate assessment of biomarker change if non-adherence to diet allocation or study procedures is greater than expected.
⇒ Women joining this study are likely to be highly motivated and the adherence may not reflect that seen in the wider general population.
⇒ Due to the small, pragmatic nature of the trial, we will not be able to formally address feasibility and cost-effectiveness versus surgical management of weight loss.

Trial registration number International Standard Randomised Controlled Trial Number Registry (ISRCTN15358157).

INTRODUCTION

The 2018 World Cancer Research Fund report concludes there is convincing evidence for positive associations between obesity and 12 cancers.[1] Breast cancer (BC) is the most common cancer of women in the UK, affecting over 54000 per year. Endometrial cancer (EC) is the fourth most common cancer in women in the UK, with around 9500 new cases in 2017 and incidence rates increasing by over 50% since the early 1990s.[2]

Maintained weight reductions of ~10% have been associated with reduced risk of postmenopausal BC (0.88 (0.79 to 09.98))

and EC (0.72 (0.54 to 0.96)).[3] Furthermore, bariatric surgery, which typically achieves an average weight loss between 20% and 30%, has been shown to reduce the risk of BC and EC by ~50%[4–6] with associated changes in endometrial cell proliferation.[7] However, bariatric surgery is unlikely to be a feasible strategy for cancer prevention due to high patient burden and upfront economic costs.

Low-energy formula total diet replacement (TDR) provides around 800 kcal/day and aims to restrict energy intake by around 60% compared with 25% energy restrictions with standard weight loss diets. A number of recent studies have demonstrated the utility of using low-energy TDR diets to achieve significant weight loss in the management of general obesity (45% participants >10% weight loss) and weight loss leading to remission of type 2 diabetes mellitus (T2DM) (46% achieved remission at 12 months).[8 9] TDR interventions are projected to be cost-effective in adults with obesity both with and without T2DM,[10] although may be less cost-effective than surgery in those with a body mass index (BMI) >35 kg/m^2.[11]

INTERCEPT (Impact of Diet-Induced Weight Loss on Biomarkers for Colorectal Cancer) studied an 8-week 800 kcal TDR in participants with a BMI >30 kg/m^2 specifically for the purpose of evaluating risk reduction of colorectal cancer. At the end of the low-energy diet period, there was an average 14% weight loss, improvements in insulin sensitivity, blood lipid profiles and significant reductions in colorectal cell proliferation, measured as Ki67 expression, in serial mucosal biopsies (mean change −43.8%; p=0.027).[12]

To date, no clinical trial has evaluated the impact of weight loss on both the breast and endometrium in combination. This pragmatic randomised controlled trial (RCT) will assess the proof of principle of a dietitian-supported TDR programme for the prevention of BC and EC in women with obesity. First, changes in cell proliferation and other cellular and molecular changes in healthy breast and endometrial tissue at the end of the 12-week low-energy diet will indicate any potential cancer risk reduction with energy restriction/weight loss in both organs. Second, dietary adherence and weight loss success throughout the 12-month intervention in both groups will inform the potential for longer-term risk reduction in this high-risk population.

METHODS AND ANALYSIS

Forty-seven female participants, at elevated risk of BC and/or EC will be recruited primarily from a high-risk BC risk prediction and prevention clinic at Manchester University National Health Service Foundation Trust (MFT) and also from staff advertisements within MFT and the University of Manchester. This study will use a non-blinded randomised controlled design with participants randomised 2:1 to either an immediate dietary intervention group (n=31) or a delayed dietary intervention (control) group (n=16). The control (delayed intervention) comparator was included to increase confidence that biomarker changes at 3 months were due to weight loss and not confounders such as variation in the time of the cycle or tissue sampling. A 12-month control group was not justified given the large body of evidence for the efficacy of TDR compared with minimal intervention standard care.[13] A 12-month control group was felt to be unethical given the requirement for four tissue biopsies, unacceptable to participants and would hinder recruitment. The 2:1 allocation to immediate versus delayed intervention was used to boost initial participation in the study.

Biopsies at the end of the 12-week TDR period will show the effects of successful short-term weight loss and the acute effects of energy restriction. Repeat biopsies at the end of weight loss maintenance would inform longer-term biomarker effects. However, these measures were not included as they would present a large burden for patients in an already intensive study.

Weight loss across the 12-month intervention will inform longer-term adherence and success of the programme in our target population of at-risk premenopausal women. A priori criteria for good adherence would be 75% of low energy days undertaken in the initial 12-week TDR and 75% retention, and 45% losing >10% weight loss at 12 months as reported in previous UK TDR trials.[9] This is important as premenopausal women often have poorer weight loss outcomes than postmenopausal women within weight loss programmes due to competing priorities, for example, child care and work.

Inclusion criteria

- Women aged 30–50 years.
- BMI ≥30 kg/m^2 or ≥27.5 kg/m^2 in the Asian group.
- Premenopausal, with regular menstrual cycles.
- Ability to use the Oviva UK app OR access to a telephone.
- Willing to follow the TDR programme using Optifast products.
- Maintain non-hormonal contraception (barrier or abstinence) until all biopsies completed.
- T2DM on diet control±metformin can be included.
- Participants must be able to read, understand and communicate in English.

Exclusion criteria

- History of BC or EC or pre-invasive breast disease.
- Hormonal contraceptive use in the preceding 3 months.
- Preventative tamoxifen or anti-progestin therapy within the last 6 months.
- Known carrier of the BRCA1 or BRCA2 gene.
- Confirmed pregnant at screening, planning pregnancy in the next 12 months or current breast feeding.
- Taking prohibited medications including: warfarin or novel anticoagulants, low molecular weight heparin or equivalent anticoagulants, antipsychotic medication, antidiabetic medication other than metformin,

orlistat or other pharmacological treatments for weight loss and steroids (more than 20 mg daily of prednisolone or its equivalent).
- Previous bariatric surgery for weight loss including gastric bypass and sleeve gastrectomy.
- Known hypersensitivity to any of the Optifast ingredients (eg, fish, milk, soy) or lactose intolerance.
- Substance abuse or harmful alcohol use as indicated by a score of 16 or above on the Alcohol Use Disorders Identification Test (AUDIT).[14]
- Diagnosis of an eating disorder, or patients with severe binge eating assessed by a score of 27 or more on the Binge Eating Scale.[15]
- Severe depression assessed by a score of 15 or more on the Patient Health Questionnaire-9 (PHQ-9).[16]
- Severe anxiety assessed by a score of 15 or more on the General Anxiety Disorder (GAD-7) questionnaire.[17]
- Participants with psychiatric or physical comorbidity or scheduled for major surgery, which in the opinion of the treating medical physician, or the chief investigator (CI), would compromise their safety or adherence to the study.

Recruitment opened in September 2020 and closed in October 2021. The planned final participant follow-up visit will be due in February 2023.

Patient and public involvement

Previous work from our group indicated that women with BMI >30 kg/m^2 were willing to lose weight (94%), eat healthily (91%) and exercise more (87%) for the purposes of primary EC prevention.[18] Prior to ethical submission, we conducted a focus group including four premenopausal women, not associated with the study or study team, at increased risk of BC to discuss the acceptability of an interventional prevention study including breast and endometrial biopsies. The women felt that paired biopsies were acceptable but expressed concerns that additional biopsies would probably dissuade them from entering the study. A second group of premenopausal women reviewed the patient information sheet and consent form.

Study objective

To determine the effects of weight loss with 12±4 weeks of TDR on cell proliferation and other cancer risk markers in the breast and endometrium of women at increased risk of BC and/or EC as compared with a usual diet control group.

Primary outcome

The change in epithelial cell proliferation (Ki67) of the breast and endometrium from baseline to 12±4 weeks after 12 weeks of TDR in the immediate diet group vs 12 weeks of normal diet in the control group.

Secondary outcomes

To determine changes in the following in the TDR group as compared with the (usual diet) control group over the 12±4 weeks between biopsies:

- Weight, body fat and fat free mass (bioelectrical impedance, Tanita MC980MA), waist and hip circumference.
- Biomarkers of cancer risk: (serum/plasma) fasting insulin, glucose, lipids, inflammatory markers, leptin, adiponectin, insulin-like growth factor-1 and DNA methylation.
- Anxiety (GAD-7 scale),[17] depression (PHQ-9),[16] quality of life (Obesity and Weight Loss Quality of Life[19] and EQ-5D-3L),[20] diet self-efficacy (Weight Efficacy Lifestyle Questionnaire Short Form).[21]
- Dietary intake (energy, protein, fat, carbohydrate, fibres) (7-day semiquantified paper food diary) analysed using Nutritics software (Dublin, Ireland).
- Physical activity (International Physical Activity Questionnaire (IPAQ) short form).[22]

To determine the following during the 12-month weight loss programme in both groups:
- Uptake and retention to the programme.
- Dietary adherence as the potential number of low energy days completed within the initial 12-week low-energy diet phase.
- Adherence to the Mediterranean diet (energy, protein, fat, carbohydrate, fibre and alcohol) from day food diaries and physical activity (IPAQ short form)[22] in the continued weight loss/weight maintenance phase.
- Anthropometric measures, cancer risk biomarkers and quality of life measures.
- Fidelity of delivery of the 12-month programme through the number and type of contacts (ie, video or standard calls, messages) and total contact time per participant for each of the dietitian, psychologist and clinician within the multidisciplinary team (MDT).
- Adverse events.

Exploratory outcomes

The impact of weight loss with the TDR versus the usual diet control group at 12 weeks on changes in:
- Markers of cellular hierarchy in breast and endometrial tissues (LGR5, SOX9, KIT).
- Progenitor populations in the breast in response to TDR using FACS (fluorescence activated cell sorting) analysis and colony formation (mammosphere) assay.
- Transcriptional changes in both the breast and endometrium using RNA sequencing.
- We will also assess any changes in mammographic density between the baseline mammogram and mammogram at the end of the 12-month weight loss programme using quantitative automated techniques (Breast Imaging-Reporting and Data System, Volpara Health and predicted visual assessment of breast density).

Trial procedures

The trial has been developed, conducted and will be reported following the Consolidated Standards of Reporting Trials guidelines.[23] Potential participants are

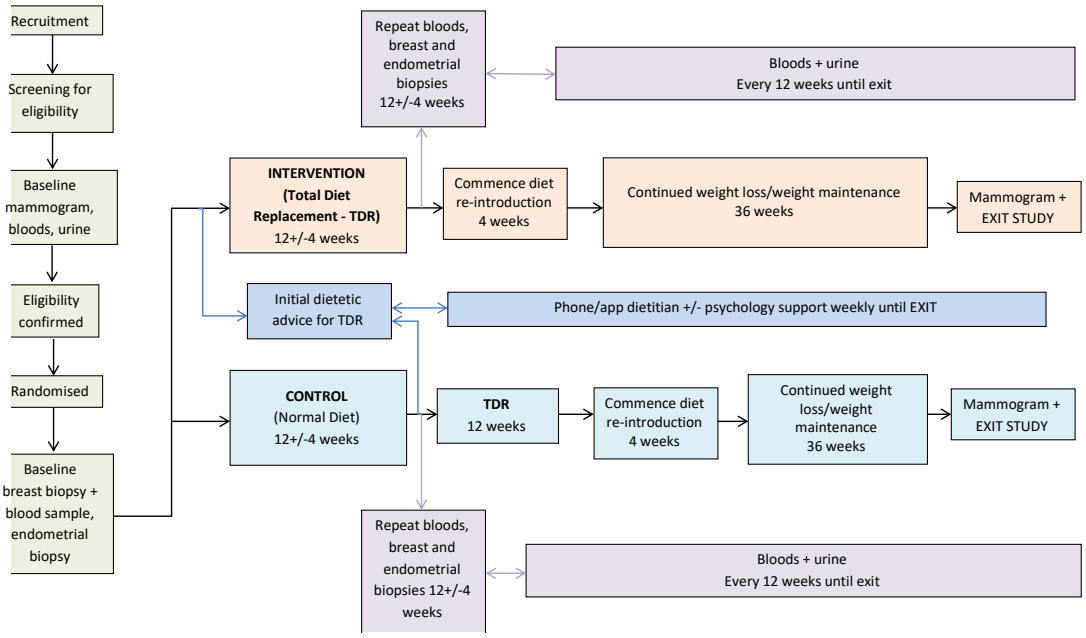

Figure 1 Study schema illustrating participant journey through the screening, total diet replacement and continued weight loss/weight maintenance phases of the study.

screened via telephone to confirm they met the required criteria for a baseline appointment. Consent is taken by a member of the trial team who is Good Clinical Practice (GCP) trained, experienced and who has been delegated by the CI to undertake this activity. Additional verbal/written consent will be obtained prior to any trial-related procedures being undertaken. Screening procedures (online supplemental information 1) will be conducted at initial consent appointment and provisionally eligible participants will receive an appointment for a mammogram (if the participant has not had one performed in the preceding 12 months). Once blood and mammogram results are available, eligible participants are randomised and baseline breast and endometrial pipelle biopsies scheduled (figure 1). All screening, biopsies and other assessments are conducted in research, breast and gynaecological outpatient clinics at MFT.

Randomisation and blinding

Eligible patients are randomised 2:1 to the immediate diet or control group by a researcher independent of the intervention using a minimisation program (Sealed Envelope, London, UK) stratified on the following criteria:

- Above or below projected median BMI of 35 kg/m^2.
- Above or below projected median lifetime risk of BC ≥17% remaining lifetime risk, with competing mortality (Tyrer *et al*).[24]

Due to the nature of the intervention, it is not possible to blind participants and clinicians to the treatment allocation. The trial endpoints will be assessed by staff who are independent from the research team delivering the intervention and where possible, they will be blinded to group allocation to minimise any potential bias. Laboratory tests will be assessed by staff who are blind to the intervention group and statistical analysis of anonymised data will be performed by staff independent from the research team to minimise any potential bias.

Study follow-up

Trial design overview is shown in figure 1. Participants from both groups will be supported weekly via the virtual platform (Oviva UK app) during the 12-month weight loss programme and will be reviewed every 3 months for assessment of weight, body composition, body measurements, diet and physical activity, quality of life and cancer risk biomarkers.

Participants may withdraw from the study at their own request or at the discretion of the CI. Withdrawal from the study will not affect patient care.

Multidisciplinary TDR weight loss programme

The programme is described in full within online supplemental information 2 and includes a TDR phase (weeks 0–12) followed by a diet re-introduction (DR) phase (weeks 12–16) and a weight maintenance/continued weight loss phase (weeks 17–52).

Participants who have attained both a weight loss of ≥15% and their target weight (which is likely to be a lower weight than that attained with a 15% weight loss) will be asked to follow their choice of either an isoenergetic intermittent or continuous weight maintenance diet. The intermittent diet includes 1 day of a food-based very low-energy diet (VLED) (~850 kcal), and 6 days of an isoenergetic Mediterranean diet. The energy content of the Mediterranean diet will be determined by the trial dietitian based on the Mifflin equation,[25] multiplied by the metabolic equivalents for their self-reported activity levels.[26] The Mediterranean diet provides 30% energy from fat (15% monounsaturated fatty acids, 8% polyunsaturated fatty acids, 7% saturated fatty acids),

25% energy from protein and 45% from low glycaemic load wholegrain carbohydrates. It includes at least five portions of vegetables andtwo portions of fruit per day, low-fat dairy products, protein foods including fish, lean meat and pulses as described previously.[27 28] Energy-controlled Mediterranean diets are considered optimum for reducing weight, blood pressure and improving lipid profiles and have been linked to lower risk of cancers including BC.[29 30] The average energy intake over the week is ~2000 kcal. Participants will be given the option of including one meal replacement product per day in the first 6 months of the programme.

Participants who have not achieved the trial weight loss goal of ≥15%, or who wish to lose more than 15%, will be asked to follow an energy-restricted intermittent or continuous energy-restricted food-based diet. The intermittent diet will involve 2 consecutive days of a food-based VLED (~850 kcal) and 5 days of an isoenergetic Mediterranean diet or 7 days of an energy-restricted Mediterranean diet. The average energy intake over the week is ~1500 kcal/day.

Relapse management for weight gain (weeks 12–52)

If participants regain ≥2 kg (from self-reported weight data), they will be advised they can either resume the initial 850 kcal TDR for 2 weeks followed by 2 weeks of DR or replace one meal per day with a meal replacement product. They will receive a booster call from the trial dietitian and additional support from the trial psychologist if required. Meal replacement products and additional support will be offered for the first two relapses, and dietitian/psychologist support only (not meal replacements) for any subsequent relapse to reduce their dependency on the TDR.

Physical activity advice and support

Physical activity advice will be delivered by the trial dietitian via phone/video call. The dietitians have previous experience and training in delivering physical activity interventions from in-house physiotherapists and a cancer exercise specialist. The trial dietitian will check the participant's responses to the Physical Activity Readiness Questionnaire (Canadian Society for Exercise Physiology)[31] to assess any contraindications to exercise. General practitioner (GP) clearance will be requested where required.

Participants who are physically capable will be asked to follow a progressive resistance exercise programme during the TDR phase, comprising one to three sets of 8–15 repetitions of arm, leg and trunk exercises three times per week over 12 weeks. Exercises are described in a written booklet and demonstrated through online videos (Physiotec, UK). Progression will be tailored to their previous level of fitness and reviewed during their calls with the dietitian. Adherence to the exercise programme is recorded from self-reporting to the trial dietitian.

After the TDR phase, participants will be encouraged to continue with the resistance exercises and also build up to between 150 and 300 minutes of moderate-intensity physical activity per week, for example, brisk walking to promote health and continued weight loss or weight loss maintenance.[32]

Psychological support

Enhanced psychology support from the trial psychologist is offered to participants described within online supplemental information 2. The psychological intervention will be centred on motivational interviewing, cognitive–behavioural therapy, behavioural activation, mindfulness skills, distress tolerance skills and emotional regulation skills.[33] Participants will be informed that specific issues disclosed to the psychologist will only be shared with the rest of the MDT with their agreement and if clinically relevant.

Remote behavioural support

Participants will receive individualised advice and will be supported remotely by their allocated dietitian and psychologist (where relevant) via the Oviva UK app or standard telephone call. The app facilitates written messages, self-monitoring of diet, weight, activity levels, blood pressure (where relevant) and an invitation to take part in peer-support group messaging on the app with other participants. Behaviour change techniques include goal setting, self-monitoring, timely personalised feedback on these records, rehearsing successful performance of behaviour, action planning and planning for how to deal with setbacks.

Protocol delivery fidelity

Dietitian support is conducted by specialist dietitians with experience of conducting dietary intervention studies using TDR and management of cancer risk. Variability in primary outcome assessments (body weight, cancer risk biomarkers) will be minimised by using calibrated equipment and quality-controlled assays.

Measurements

The measurements taken at each stage of the PROBE-TDR (PRevention Of Breast and Endometrial cancer using Total Diet Replacement) Study are detailed in online supplemental information 3.

Physical measurements

Patients will be asked to abstain from alcohol and moderate physical activity for 24 hours prior to their appointment and be asked to attend in the fasted state (minimum 8-hour fast) but allowed plain water.

Height will be measured to the nearest millimetre, with the Frankfort horizontal plane, using a portable stadiometer (Chasmors, London). Body weight will be measured to the nearest 0.1 kg in light clothing, without shoes or socks, using calibrated bioimpedance scales (Tanita MC980MA) using a standardised protocol.[34] Waist circumference is measured across the umbilicus and hip circumference will be measured over the participant's underwear at the widest point over the buttocks to the nearest 0.5 cm.

Seated blood pressure will be measured in triplicate at rest with legs uncrossed for at least 10 minutes.

Blood and urine sampling

This will be performed at baseline to include: fasting insulin, glucose and lipids, leptin, adipokines, inflammatory cytokines including C-reactive protein and HbA_{1c}. These will be repeated after 12±4 weeks of intervention/control and at 6, 9 and 12 months for both groups and month 15 for the control group. HbA_{1c} will only be repeated at the end of the TDR phase and 6 months post-TDR to limit costs. Bloods for oestrogen and progesterone will be taken at the time of the breast biopsies only. Urine samples will be obtained at screening and repeated at each 3-month visit for pregnancy testing and storage for potential future metabolomic analysis.

Breast and endometrial biopsies

Baseline vacuum-assisted breast biopsy and blood sampling for oestrogen and progesterone will be undertaken in the luteal phase (week before expected menstruation) of the menstrual cycle; endometrial sampling will be undertaken in the follicular phase (week following menstruation) of the menstrual cycle. The biopsies will be obtained by study clinicians and the bloods by research staff. Breast and endometrial biopsies will be repeated after at least 8 weeks of TDR/usual diet in the same phases of the menstrual cycle as the baseline tests. Participants are recruited with a history of regular menstrual cycles. During the first 3 months of the study, they self-report their menstrual pattern to researchers over two to three cycles to facilitate scheduling of the endometrial biopsies within the follicular phase of their cycle. The phase of cycle is then confirmed through an assessment of endometrial morphology by a pathologist. Participants in the immediate dietary intervention group will remain on the TDR until they have undergone their post-TDR breast and endometrial biopsies. Some participants may need to remain on TDR for up to 16 weeks if there are difficulties scheduling the repeat matched biopsies in line with their menstrual cycles.

Laboratory analyses

Change in proliferation from baseline to 3 months will be assessed by percentage epithelial Ki67 expression in the paraffin-embedded tissue sections. Breast samples will be digested to single cell suspension and processed for mammosphere assay to provide readout of stem cell/early progenitor activity. FACS analysis of the proportion of luminal progenitors (CD49f+/EPCAM+), differentiated luminal (CD49f–/EPCAM+) and myoepithelial (CD49f+/EPCAM–) stem cells will determine the change in cell proportions with TDR versus controls. RNA sequencing will be performed on the breast and endometrial tissues to evaluate gene expression changes owing to weight loss.

Sample size

Many RCTs with a continuous outcome adjust for the same variable at baseline using an analysis of covariance (ANCOVA). Thus, using summary data within the Breast Cancer Anti-Progestin Prevention Study (NCT02408770), in which premenopausal women also underwent luteal phase breast biopsies, we can use the mean (SD) luteal breast Ki67 as 4.99 (5.03) together with the sampsi command in STATA with the following code settings: *sampsi 2.5 4.99, sd(5.03) pre (1) post(1) r01(.86) ratio(2) p(0.8)*. This code uses the two means 4.99, 2.5 (reflecting a 50% difference), a common SD of 5.03, a 2:1 allocation, a baseline correlation of 0.86 and power of 80%. With 13 controls and 26 subjects in the intervention group, the study will have 80% power at a 5% significance level to detect an adjusted mean difference in Ki67 at 3 months within the breast and endometrial biopsy samples. A difference of 50% or more in change in Ki67 between the control and intervention group has been chosen as this represents a clinically meaningful effect size for a mechanistic study.[35] Incorporating a 20% loss to follow-up rate, the sample size increases to 16 controls and 31 in the intervention group.

Statistical analysis

The primary data analysis for change in Ki67 will be by intention to treat using ANCOVA with a 5% level of significance. This will be an unadjusted analysis comparing the outcome measured, controlling for the baseline value. We will also carry out a per-protocol analysis as a secondary analysis. Missing data will be imputed via multiple imputation methods. The analysis will be conducted using SPSS 28.0.1.0 and STATA.

Data analysis of the secondary endpoints will be by intention to treat and will not undertake any significance tests to compare the groups. Change scores (95% CI) for the secondary outcomes will be presented from within and between both groups. To determine secondary endpoints of changes in lifestyle/weight loss over time, linear mixed modelling will be used to assess the degree of change over time.

We will assess engagement with the TDR weight loss programme from the receipt of calls and use of Oviva app functions, for example, self-monitoring.

Data management

The source data which comprise medical notes, electronic data sources (Oviva app, Nutritics), case report form (CRF) and copies of the participant-completed questionnaires are the primary source data. Participant data will be anonymised and will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act (2018) and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations (2006) as defined in the Kings Health Partners Clinical Trials Office Archiving SOP (17 Data Management). Deidentified data will be stored in a study-specific Research Electronic Data Capture database. The sponsor will periodically audit the site study file, a sample of CRFs, consent forms and source

Table 1 Summary of ethical amendments

Protocol	Date	Summary of changes
V.4	29 April 2021	Collection of diet-related side effects to include control group. Offer use of Nutritics app to allow remote function for recording 7-day food diary. Additional clinicians/research study staff.
V.3	14 October 2020	Amendment to wording of patient information sheet cover letter to reflect remote review of patients during the COVID-19 pandemic.

data and accuracy of the study database to ensure satisfactory completion.

Patient safety

Antihypertensive and diuretic drugs will be stopped on the day TDR is commenced for those who take these medications due to a pre-existing diagnosis of hypertension. This is a safety measure, because blood pressure is likely to fall on the diet due to rapid changes in weight. Individual clinical decisions may be necessary for a person's best interest. In keeping with the recommendations for medicines management within the DiRECT Study,[8] those whose medications have been stopped will be monitored weekly using a home monitor and the participant can input their result within the Oviva app for the study clinician to review. Medication(s) for managing blood pressure will be re-introduced if clinically required (online supplemental information 4) and communicated to the GP.

Participants taking metformin will be advised to remain on this medication for the duration of the study.

Adverse events will be monitored and graded monthly during the TDR phase for both groups, also during the normal diet phase for the control group using the National Cancer Institute CTCAE V.5.0.[36] This will indicate rates of potentially TDR-associated and background rates of adverse events. Serious adverse events will be reported to the Research Ethics Committee (REC) and sponsor and documented within the participants' medical record.

Study management

The study management group comprises the CI, project manager, clinical research fellow, radiology team, dietitian and psychologist, who will jointly monitor study conduct and progress. All aspects of the study and all study personnel will adhere to the study protocol (V.4.0 or subsequent approved version) and GCP and Data Protection principles. Regular team meetings will ensure quick resolution of recruitment issues, study processes and data collection inconsistencies.

ETHICS AND DISSEMINATION

This study was adopted onto the National Institute for Health Research trial portfolio on 22 April 2020 and is sponsored by the MFT. Any planned modifications to the protocol will be approved by the REC before they are adopted into the study. An audit trail of ethical amendments and documentation will be kept to allow monitoring by the research team and external regulatory bodies (table 1). The study was registered with an International Standard Randomised Controlled Trial Number on 11 May 2020.

Results will be disseminated through publication in peer-reviewed scientific journals, presentation at conferences and via charity websites.

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Contributors SH and EJC are the principal investigators. MH, RC, AH, SH and EJC all contributed to the design of the study. HC is responsible for the day-to-day running of the study, patient recruitment and consent and collection of gynaecological tissue samples. SH and EJC provide study oversight and with BGI, provide clinical guidance. MH and CL are responsible for delivery of the dietetic component of the study. AJM, YYL, CP and SP are responsible for the collection of breast tissue samples. SK is responsible for study administration and data collection. KS contributed to protocol development and achieving ethical approval. HH is involved in scientific analyses of breast tissue samples. JW is responsible for the psychological intervention and JB developed the statistical basis for the protocol. HC drafted the initial manuscript. All authors critically reviewed and revised the manuscript and have read and approved the final version and contributed to the development and set-up of the study.

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Disclaimer The funders of the study had no role in the study design or writing of the report.

Competing interests All authors declare no competing interests. MH and BGI have received research funding for previous research associated with Nestle Health Care and Oviva, but no financial benefit from this research study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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