Study Title: Pre-operative intentional weight loss to support post-operative recovery in patients with overweight and endometrial cancer: the ENDO-CARE feasibility randomised controlled trial

Short title: Could supported weight loss reduce womb cancer surgery complications?

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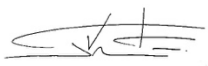
Chief Investigator:	Dr Dimitrios Koutoukidis, Senior Research Fellow, Nuffield Dept. of Primary Care Health Sciences, University of Oxford
Co-chief investigator:	Prof Emma Crosbie, Professor and Honorary Consultant in Gynaecological Oncology, Division of Cancer Sciences, University of Manchester
Investigators:	Prof Susan Jebb, Professor of Diet and Population Health, Nuffield Dept. of Primary Care Health Sciences, University of Oxford
	Prof Claire Foster, Professor of Psychosocial Oncology, Centre for Psychosocial Research in Cancer, University of Southampton
	Prof Simon Buczacki, Richard Blackwell Pharsalia Professor of Colorectal Surgery, Nuffield Dept. of Surgical Sciences, University of Oxford
Sponsor:	University of Oxford
	Joint Research Office, Churchill Drive, Headington, Oxford OX3 7GB
Funder:	National Institute for Health and Care Research

Chief Investigator Signature: 

Statistician Signature: 

Conflicts of interest: DK and SAJ report being investigators in two publicly-funded (NIHR) trial where the weight loss intervention was donated by Nestle Health Science and Oviva to the University of Oxford outside the submitted work. No other conflicts of interest are reported.

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

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1. KEY CONTACTS

Chief Investigator	Dr Dimitrios Koutoukidis Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG T: +44 (0)1865 617767 E: dimitrios.koutoukidis@phc.ox.ac.uk
Sponsor	University of Oxford RGEA, Joint Research Office, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB T: +44 (0)1865 616480 E: rgea.sponsor@admin.ox.ac.uk
Funder(s)	National Institute for Health and Care Research Ryan Wolstenholme, Programme Manager, NIHR Academy T: +44 (0)113 5328 461 E: academy-awards@nihr.ac.uk
Clinical Trials Unit	Surgical Intervention Trials Unit, University of Oxford T: 01865 223491, E: situ@nds.ox.ac.uk
Statistician	Martyn Hill, MSc E: martyn.hill@nds.ox.ac.uk
Committees	Trial Steering Committee Chair: tbc Trial Management Committee Chair: Dr Dimitrios Koutoukidis, T: +44 (0)1865 617767 E: dimitrios.koutoukidis@phc.ox.ac.uk

2. LAY SUMMARY

In the UK, about 10,000 women are diagnosed each year with womb cancer. It is the most common gynaecological cancer. Surgery to remove the cancer is the best treatment. However, it has a risk of complications, which is higher for people with overweight/obesity. Patients experiencing complications recover more slowly, stay in hospital longer, and need more care. This isn't good for patients or the NHS.

Physical fitness and well-controlled blood sugar are linked with fewer complications from surgery. For people with overweight, weight loss improves both of these factors, so it may reduce complications. One reliable way to lose a meaningful amount of weight in the short period before surgery (3-4 weeks) is through a low-calorie diet programme: eating only special nutritious soups and shakes (800 calories/day) that have all the necessary vitamins. With weekly support from a dietitian, most people succeed. Typically, people lose 5% of their weight within 20 days. The NHS uses a version of this programme to treat type 2 diabetes.

In small-scale studies, patients with cancer and overweight have been willing and able to take part in less intensive weight management programmes before surgery, but lose little weight. However, the period before womb cancer surgery is associated with feelings of uncertainty and anxiety, so it is unclear if patients can follow a more intensive programme.

To start to find out if this treatment is in the best interests of patients' physical and mental health, we will recruit 72 patients with overweight awaiting womb cancer surgery. Half will be randomly allocated to continue with their usual care and half will be offered the weight loss programme. We will see whether enough patients are willing to take part, lose weight, and return for follow-up visits. We will monitor complications for 30 days after surgery and any reduction in muscle mass as a result of the weight loss. We will interview staff and patients in the intervention group about their experience.

This information will tell us if a full trial is worthwhile to test whether this programme can reduce complications from surgery, improve outcomes for patients with womb cancer, and if the financial costs are likely to be worth the benefits. It will also help us refine the treatment plans according to patient feedback.

We will publish results in scientific journals and talk to clinicians and to patients with cancer supported by professional groups and charities (e.g., Macmillan, Peaches Womb Cancer Trust). Our patient group will help us to explain the results clearly.

3. SYNOPSIS

Study Title	Pre-operative intentional weight loss to support post-operative recovery in patients with overweight and endometrial cancer: the ENDO-CARE feasibility parallel randomised controlled trial
Short title	Could supported weight loss reduce womb cancer surgery complications?
Study registration	To be registered with ISRCTN.
Sponsor	University of Oxford RGEA, Joint Research Office, Churchill Drive, Headington, Oxford OX3 7GB T: +44 (0)1865 616480 E: rgea.sponsor@admin.ox.ac.uk
Funder	National Institute for Health and Care Research
Study Design	Multi-centre feasibility parallel randomised controlled trial with embedded process evaluation
Study Participants	Adults with overweight awaiting endometrial cancer surgery
Sample Size	72 (36 per arm) and around 16 research/clinical staff
Planned Study Period	Planned start date: 01/09/2023 Planned end date: 29/02/2028 Individual participant's involvement: approx. 2-3 months Long-term follow-up via medical records: up to 3 years
Planned Recruitment period	September 2023 to January 2025

Outcomes	Objectives	Outcome Measures	Timepoint(s)
Primary	1. To assess whether progression to a definitive RCT is justified	i. Recruitment rate ii. Engagement rate iii. Adherence rate iv. Retention rate v. Safety profile	i. Screening ii. Throughout the intervention iii. Throughout the intervention iv. Pre-operative assessments and 30 days post-operatively v. Throughout the trial
Secondary	To report between-group differences in 1. Morbidity 2. Oncological outcomes	i. Any morbidity ii. Morbidity by grade (I, II, IIIa, IIIb, IVa, IVb) iii. Survival (grade V)	i.-ii. Discharge and 30-days post-operatively iii: Discharge, 30-days post-operatively, 3 years

Outcomes	Objectives	Outcome Measures	Timepoint(s)
		iv. Fitness to receive planned adjuvant therapy	iv. 30-days post-operatively
		v. Recurrence	
	3. Operative outcomes	vi. New primary/ secondary cancer	v-vi: 3 years
		vii. Intraoperative blood loss	vii-ix: Discharge
		viii. Operative time	
		ix. Conversion to open surgery	
		x. Surgical site infection	x-xi: Discharge and 30-days post-operatively
		xi. Time in intensive care unit and high dependency unit	
		xii. Re-operation rates	xii-xiii: 30-days post-operatively and 3 years
		xiii. Re-admission rates	
	4. Hospital stay	xiv. Length of hospital stay (fitness to discharge)	xiv: Discharge
		xv. Days alive and out of hospital	xv: 30-days post-operatively
		xvi. Weight	
	5. Anthropometry	xvii. Fat-free mass	xvi-xvii: Baseline, pre-operative assessment 3, and 30 days post-operatively
	6. Fitness	xviii. Time for sit-to-stand test	xviii: Baseline, 30 days post-operatively
		xix. EQ-5D-5L	
	7. Health-related quality of life (HRQoL)	xx. HADS	xix-xx: Baseline, pre-operative assessment 2 and 30 days post-operatively
		xxi. EORTC-QLQ-EN24	xxi: 30 days post-operatively
		xxii. Intervention costs	
	8. Costs and resource use		xxii: End of intervention
		xxiii. Healthcare resource use	xxiii-xxiv: Baseline, 30 days post-operatively
		xxiv. QALYs	
		xxv. Adverse events	
	9. Adverse events		

Outcomes	Objectives	Outcome Measures	Timepoint(s)
			xxv: Baseline, pre-operative assessment 3 and 30 days post-operatively
Process	To examine the 1. Experience of the intervention	i. Analysis of qualitative interviews with intervention participants ii. Feedback pre-operatively iii. Feedback post-operatively	i. Pre-operative assessment 1 ii. Pre-operative assessment 2 iii. 30-days post-operatively
	2. Experience of the trial	iv. Feedback post-operatively v. Interviews with staff	iv. 30 days post-operatively v. Throughout the trial
	3. Control group contamination	vi. Feedback post-operatively	vi: 30 days post-operatively
	4. Fidelity of delivery	vii. Observation of consultations	vii: Throughout the intervention
	5. Barriers to trial enrolment	viii. Reasons for declining participation	viii. Screening
Intervention(s)	Low-energy total diet replacement programme with behavioural support		
Comparator	Care as usual		

4. ABBREVIATIONS

ASA	American Society of Anaesthesiologists
BMI	Body mass index
CI	Chief Investigator
eCRF	Electronic Case Report Form
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EORTC-QLQ-EN24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial cancer module
EQ-5D-5L	EuroQoL-5D 5-level version
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
HRQoL	Health-related quality of life
ICF	Informed Consent Form
NHS	National Health Service
NIHR	National Institute for Health and Care Research
RES	Research Ethics Service
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised controlled trial
R&D	NHS Trust R&D Department
RGEA	Research Governance, Ethics & Assurance Team
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
QALYs	Quality-adjusted life years

5. BACKGROUND AND RATIONALE

Endometrial cancer is the most common gynaecological cancer and fourth most common cancer in women affecting about 10,000 women each year in the UK. Endometrial cancer is the cancer most strongly linked with obesity, with 62% higher risk of developing the cancer for every 5 units increase in body mass index [1]. Following endometrial cancer surgery, obesity significantly and independently increases post-operative morbidity, such as the total number of complications and wound infections.[2, 3] This leads to longer recovery for patients and higher costs for the healthcare system.[4]

Guidelines for any pre-operative treatment are weak due to low-quality evidence.[5, 6] In two James Lind Alliance priority setting partnerships (for peri-operative care and for people living with cancer), finding effective pre-operative treatments and preventing surgical complications were among the most important research questions.[7, 8]

Pre-operative intentional weight loss in patients with overweight awaiting endometrial cancer surgery could reduce post-operative morbidity by improving physical function, cardiovascular fitness, systemic inflammation, and glucose regulation.[9-14] The amount of weight loss needed to improve morbidity outcomes in other conditions follows a dose-response pattern. Evidence drawn from bariatric surgery studies consistently shows that 5-9% and ≥10% pre-operative weight loss is independently associated with 31% and 42% lower 30-day mortality, respectively.[15]

In the endometrial cancer setting, weight loss needs to be achieved within the typical 4-week window between decision to treat and surgery. The most reliable and scalable way to achieve this is through a nutritionally-replete, high-protein, low-energy total diet replacement programme with behavioural support (TDR). TDR reliably leads to a mean 7% (SD: 1.8kg) weight loss within 4 weeks in diverse populations with obesity-related diseases, including in older adults with moderate frailty and with atrial fibrillation, and implemented in pragmatic settings.[16-25] A longer version of the programme is currently being tested nationally in the NHS with the aim of remission of type 2 diabetes.[26]

Intentional weight loss is strongly linked with intervention adherence.[27] However, the period around cancer diagnosis is associated with feelings of stress and anxiety.[28, 29] In this context, it is unclear if people with cancer will enrol and adhere to this intensive intervention to the same extent as in less uncertain chronic disease settings. On the other hand, the structured nature of a nutritionally replete dietary intervention may give people a sense of control and empowerment.[30, 31] Patients report their cancer diagnosis being a stimulus for healthier dietary change,[32, 33] but also report making only marginal changes on their own.[34] This highlights the need for support. Small single-arm and randomised trials have shown high feasibility of recruitment (~50%), engagement (~90%), and retention (~85%) to less intensive pre-operative dietary weight loss interventions in breast, prostate, and gastric cancers. These programmes advised an energy-restricted healthy diet or provided partial meal replacements.[35-38] Whilst these approaches support the feasibility of intervening in the pre-operative cancer setting, they achieved only small weight loss (average: 3kg) with high variability (SD: 4-5kg) that may be insufficient to improve surgical outcomes.

There are theoretical concerns about muscle mass loss. However, the amount of body fat is positively associated with the amount of muscle mass.[39, 40] During *intentional* weight loss, muscle mass reductions are small (~1%),[41, 42] likely not clinically meaningful,[43, 44] and, in older adults, weight

loss significantly improves physical and cardio-metabolic fitness.[9, 45] Another trial of very low energy diet in older adults aged 65-85 years showed improvements in physical function without adverse outcomes despite small reductions in lean mass.[24] We have also replicated these changes in body composition in our ongoing trial of TDR in patients with obesity and advanced liver disease, who are moderately frail, with no adverse outcomes.[21] Unlike some weight loss programmes, TDR, being micronutrient-rich, can improve general nutritional status,[24, 46] which may further contribute to beneficial outcomes.[47, 48]

Accordingly, pre-operative TDR may improve outcomes in this population but this hypothesis needs formal testing. A pilot trial with a nested qualitative component is required to estimate recruitment, engagement, adherence, and retention before a trial testing the intervention's effectiveness and cost-effectiveness can be realised.

Adoption of effective interventions into practice depends critically on cost-effectiveness. Typically, prehabilitation before cancer surgery has involved logistically complex and resource-intensive interventions, such as inclusion of multi-disciplinary services, multiple face-to-face appointments, need for space and equipment in hospitals, and significant travelling to hospitals by patients. From a health services and social services perspective, such interventions would need to be very effective in reducing post-operative complications to be cost-effective. Currently, no such intervention has met these criteria.

The relatively low cost of a 4-week TDR programme [total approx. £440/patient comprising £240 for dietetic support, £200 for food products based on previous cost-effectiveness analyses][49, 50] might make this intervention cost-effective. We will estimate potential costs and benefits during the pilot and determine the necessary resources (e.g., intensity of behavioural support) to guide the future definitive trial.

6. OBJECTIVES AND OUTCOME MEASURES

Please refer to objectives and outcomes in section 3.

7. STUDY DESIGN

This is a prospective randomised controlled trial (RCT) with an embedded process evaluation to assess the feasibility of progression to a definitive RCT. Participants will be recruited from hospitals across England.

Participants are expected to be involved in the study for approximately 2-3 months. They will be asked to attend hospital visits for screening, pre-operatively (on the day of admission), and 30 days post-operatively. They will also remotely complete questionnaires at 1-3 days pre-operatively. Those in the intervention group will have a semi-structured qualitative interview over the phone. The intervention will be delivered over the pre-operative period. Appendix A shows the study flow-chart.

Clinical and research staff involved in the study and recruitment process will also be interviewed The specific content of the staff interview is in Appendix D. Participants will have a remote interview (i.e. over the phone / via MS Teams).

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants (patients)

Participants with BMI ≥ 28 kg/m^2 listed for endometrial cancer surgery aged ≥ 18 years.

8.1.1. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Able to communicate in English or has a relative/friend/carer acting as interpreter.
- Aged 18 years or above.
- BMI ≥ 28 kg/m^2 (or BMI ≥ 25 kg/m^2 for people of Black, Asian, or minority ethnic origin).
- Planned for curative elective surgery for endometrial cancer.
- Performance status 0-2.

8.1.2. Exclusion Criteria

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

- ≥10% self-reported weight loss in the 6 months before the screening visit
- <20 days from the screening visit until surgery.
- Having allergy to soy.
- Documented stage 4-5 kidney disease.
- Documented severe heart failure (defined as New York Heart Association grade 3 or 4).
- Previous bariatric surgery.
- Type 1 diabetes.
- Currently on insulin with a previous episode of diabetes ketoacidosis.
- Currently on warfarin.
- Pregnancy, breastfeeding, or planning pregnancy during the course of the trial.
- Any other significant disease or disorder which, in the opinion of the Investigator or healthcare professional, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Currently taking part in other interventional clinical trials unless agreed in advance by all trial teams (participation in observational studies is allowed).

A list of trials that co-enrolment has been agreed by all trial teams and a list of trials that co-enrolment has been agreed to not be allowed will be regularly updated and provided to trial sites.

8.2. Study Participants (staff)

Any research and clinical staff involved in the study and recruitment process. There are no specific exclusion criteria.

9. PROTOCOL PROCEDURES

A schedule of procedures is available in Appendix B.

9.1. Recruitment

Participants will be recruited from NHS Trusts across England. We will aim to select sites to cover multiple geographical areas. Sites need to meet the following criteria:

- Assign a named healthcare professional (surgeon, anaesthetist, nurse, or dietitian) as local Principal Investigator
- Train staff to the trial procedures
- Have adequate staff and resources to
    - recruit participants, conduct study assessments, and provide relevant research data (including a blinded researcher for outcome assessment)
    - liaise regularly and as appropriate with the Surgical Intervention Trials Unit and central study team, and
    - commit to a minimum target recruitment rate of 3 patients every 4 months (0.75 patients per month).

The recruitment pathway will be flexible within and across recruitment sites to allow for differences in cancer diagnostic and treatment pathways across patients and hospitals. In all cases, a member of the clinical team will be the first person who will raise the option of the research study to a potentially eligible participant before that participant is formally approached by a member of the research team to discuss entering the trial.

Patients may be approached about the trial before or after the final decision to have surgery has been made to allow for as much time as possible for potential participants to consider participation. However, they will only enrol after a provisional plan has been made for surgery. For example, when cancer is suspected during routine checks, a member of the clinical team (e.g., the cancer nurse specialist or doctor) will inform the patient about the possibility of a cancer diagnosis and the likelihood of surgery. At this time, they will make patients aware of the trial and ask them for their verbal consent to pass their contact details to the research team. The member of the clinical or research team will provide the potential participant with a participant information sheet (PIS). A research nurse (or other member of the research team) will contact the participant to discuss the study and pre-screen potentially eligible participants with a brief phone interview to check the eligibility criteria and concomitant medication. Once the endometrial cancer diagnosis is confirmed, a research nurse (or member of the clinical or research team) will contact the potential participant for a second discussion about the trial and to book them in for a screening visit. In other cases, the first contact of a potential participant with the research nurse might be after the endometrial cancer diagnosis has been confirmed by the clinical team or after potential participants have discussed the surgical treatment options with a member of the clinical team and a decision to treat has been made.

In hospitals where participants are notified in advance that research studies are taking place and their personal information may be accessed by the research team, a research nurse (or member of the research team) may also screen relevant clinic lists and/or observe the multidisciplinary team meeting where surgical cases are discussed to flag potentially eligible participants to the clinical team.

We will create a video covering the key points of the PIS, upload it online, and direct participants to the video link to facilitate accessibility.

The screening visit should be booked within the next working day (and up to 3 days) following communication to patient that there is a (provisional) plan for surgery.

Participants who decline to participate will be asked to provide the reasons for declining to take part by choosing all possible reasons from the following pre-defined list. This information is likely to be provided over the phone to the member of the clinical or research team and will be retained for the study without any personal identifiers (anonymously).

1. I would find it difficult to stick to the diet
2. I do not like the idea of eating shakes and soups instead of usual food
3. I am worried about potential side effects from the diet
4. Transport / distance to hospital
5. I feel unable to cope with additional requirements of me at this moment in time
6. I do not like the idea of randomisation
7. I feel uncertain that the trial will benefit me
8. I was not given adequate information
9. Other

A purposive subsample of research and clinical staff will be invited for a 45-minute qualitative interview. This includes any research and clinical staff involved in the study and recruitment process. A member of the central research team will email local staff inviting them to take part in the study. Staff will be given an information sheet and provide informed consent prior to interview.

9.2. Informed Consent

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

Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information (with no minimum time limit), and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Electronic written informed consent will then be obtained by means of electronic participant-dated signature and dated signature of the person who presented and obtained the informed consent on the eCRF. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal

Investigator. A copy of the signed informed consent will be given to the participant (via email or printed physical copy). The original signed form will be retained in the eCRF. For trial participants, a further copy will be saved in their medical records.

9.3. Screening and Eligibility Assessment

During the screening visit, participants will provide written informed e-consent. Following informed consent, their weight and height will be measured to ensure they meet the BMI criterion. The concomitant medication will be reviewed. Each participant must satisfy all the approved inclusion and exclusion criteria of the protocol. If a participant does not meet all of the criteria, they will be recorded as a screen failure. Participants will also complete all baseline assessments.

9.4. Randomisation

The randomisation software will be programmed by the clinical trials unit. There will be no paper-based back up randomisation procedure in case of emergencies.

At the end of the screening visit, participants who meet all the eligibility criteria and are keen to proceed with the study should be randomised. Queries on eligibility must be resolved before randomisation and participants who do not meet all the eligibility criteria must not be randomised. The research nurse or delegate will randomly allocate participants using a web-based central minimisation software. Eligible participants will be individually randomised with a 1:1 allocation ratio to receive either the intervention or care as usual through minimisation with a 20% random element. The two stratified variables will be BMI (</≥40 kg/m^2) and median age at diagnosis ((</≥65 years).

The research nurse will enter the participant details to the randomisation system (initials, participant ID and research site code, confirmation of eligibility, confirmation of completion of baseline assessments, date of informed consent, and stratification factors). The system will allocate the participant and instantly inform the researcher of the allocation. The researcher will then inform the participant of their allocation.

The maximum duration between completion of the screening visit and randomisation will be 24 hours (e.g., to allow for query resolution). In such case, the local research team will contact the participants to notify them about their allocation.

If randomisation has not occurred within 24 hours but participants are still keen to continue with the study, they will have to be re-screened by checking that the time limit until surgery has not elapsed but participants will not be required to complete again the baseline assessments.

Allocation concealment is achieved as randomisation occurs after the baseline visit, the randomisation algorithm is unmodifiable and concealed from investigators and the local research teams, and the local research teams have no access to the total number of participants randomised to each group.

Following randomisation, the research team will send a letter to the participant's GP informing them about trial participation and group allocation.

9.5. Blinding and code-breaking

It is impossible to blind the participants and research nurses due to the nature of the intervention. Therefore, procedures for breaking the allocation code are not applicable. However, the assessors of the future primary outcome (research nurses conducting the post-operative follow-up visit) will be blinded.

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

9.6.1. Description of study intervention(s)

The intervention is a low-energy total diet replacement programme with behavioural support.

Participants will replace all their foods with a nutritionally complete package of 4 formula products per day (such as soups and shakes (~800kcal/day)). The composition will follow regulatory guidelines.[51]

They will be advised to drink >2.5L/day of energy-free fluids (e.g., water, tea, coffee, diet soft drinks) with a provision of up to 100ml of skimmed milk for tea/coffee per day but no energy-dense drinks (e.g., alcohol).

Participants will have a 45-min introductory phone call with a dietitian to provide behavioural support and then weekly 20-minute follow-up calls. Participants will be offered the option of having the support over video (MS Teams) if they prefer. The support aims to maintain motivation during the adjustment to formula foods and problem-solve issues that arise. This is a structured programme using weekly progress review, feedback on changes, checks on product tolerance, practical tips for mixing shakes and adding flavour, problem solving any barriers, managing social situations, coping with hunger, encouragement, action planning, avoiding and managing lapses, and behaviour change techniques to maintain motivation. In previous studies the support has been valued highly by participants.[31, 52]

The intervention will start on the day post-randomisation. Following randomisation, research nurses will provide participants products, so that they can start the programme the next day. The introductory phone call with the dietitian should ideally be completed on the day of or the day following randomisation. Participants may receive additional products by post if necessary. The intervention will finish the day before surgery.

One in 5 people experience an adverse, mostly mild, event due to the intervention.[16] Constipation (1 in 7), fatigue (1 in 12), headache (1 in 17), and dizziness (1 in 22) are the most common Adverse events (AEs) albeit mild (only 11% were moderate or severe), reduce in intensity over time and disappear as soon as the intervention is discontinued.[16, 17] Here, the risk of constipation will be proactively managed with advice for high energy-free fluid intake (>2.5 litres/day) and a fibre supplement.

Participants will receive the intervention on top of the local standard care pathway that may include advice and support on pre-habilitation.

Medication adjustment

Type 2 diabetes: As per the NHS England and NHS Improvement guidance for this intervention, participants who are managing their diabetes with sulfonylureas (gliclazide, glibenclamide, glimepiride), meglitinides (Repaglinide, Nateglinide), or SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin) will be instructed to stop them on the first day of the intervention due to safety risks, including the risk of hypoglycaemia (sulfonylureas, meglitinides) or risk of ketoacidosis (SGLT2 inhibitors).

If participants do not stop these medications, they must not start the intervention. Adjustments on insulin will be based on a locally agreed guidance and participants must follow these adjustments to continue with the intervention. Participants will be required to continue attending their diabetes review appointments /monitoring at their GP as usual and to notify their GP if they disengage from the intervention (as medication may need to be restarted).

Hypertension: If the blood pressure at the screening visit is uncontrolled (If blood pressure is considered uncontrolled at time of referral (systolic ≥ 140mmHg OR diastolic ≥ 90mmHg), no changes to blood pressure lowering medications will be made.

If the blood pressure at the screening visit is controlled (both systolic <140mmHg AND diastolic <90mmHg), one blood pressure medication should be adjusted on the first day of the intervention. Medication being used specifically and solely for managing blood pressure, in a particular participant, are the priority for adjustment. The agent that has been added last according to current NICE (National Institute for Health and Care Excellence) guidance should be stopped. If not being used for other indications, this would be (in order of stopping first):

a. Spironolactone or alpha blocker or beta blocker
b. Thiazide diuretic (or calcium channel blocker)
c. Calcium channel blocker (or thiazide diuretic)
d. Angiotensin-converting enzyme inhibitor or Angiotensin receptor blocker

If the patient is taking medications which affect blood pressure but ALL are being used for other indications (i.e., none are being used solely to manage blood pressure), clinical judgement and shared decision making should be used taking into account the blood pressure reading. In this case, the dose should be cautiously reduced (e.g., to the next lower dose) instead of stopped.

Self-monitoring of blood pressure and blood glucose

Intervention participants taking insulin or medication for hypertension will be asked to self-monitor their blood glucose or blood pressure, respectively, and report out of range values to the dietitian who will communicate this to the participant's GP within 3 working days (or earlier if deemed necessary). Participants will be counselled about symptoms of hypoglycaemia and postural hypotension and advised of when and how to seek appropriate support. They will receive blood pressure/glucose monitors if they do not own one.

9.6.2. Description of comparator

Participants will follow the local standard care pathway that may include advice and support on pre-prehabilitation.

9.6.3. Cancer waiting times

NHS Cancer Waiting Times Monitoring Dataset Guidance gives strict requirements for time to first definitive treatment date for curative endometrial surgery. As per the latest guidance and another national pre-habilitation trial in the field, the date of consent given by a participant to be entered into the trial will be the first definitive treatment date for this purpose in line with the above guidance [53,

54]. The pre-operative intervention part of this study has been designed to fit within the targets of cancer waiting times guidance. Surgery should not be unduly delayed as a result of entry into the study.

9.6.4. Description of study procedure(s)

Demographic questionnaire – 2 mins

Basic demographic characteristics including date of birth and ethnicity will be captured using standardised questions. Contact details (home address, contact number(s), GP practice address, next of kin) will be extracted from medical records and verified by the patient.

EuroQoL-5D 5-level version (EQ-5D-5L) questionnaire – 5 mins

Widely used and validated general HRQoL instrument assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression as well as overall self-rated health.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial cancer module (EORTC-QLQ-EN24) – 10 mins

Widely used and validated HRQoL instrument assessing functional status and symptoms post-operatively specifically following endometrial cancer.

Hospital Anxiety and Depression Scale (HADS) – 5 mins

Widely used and validated anxiety and depression questionnaire.

Resource use questionnaire – 5 mins

A modified Client Service Receipt Inventory [55] will be used to collect data on use of primary care services, social care services, and other health care professional, as well as time off work.

Concomitant medication (5 min)

Participants will be asked to bring their prescription or a list of their medication at the screening visit for these to be recorded.

Weight and body composition – 3 mins

Weight will be measured barefoot and with light clothing to the nearest 0.1kg using a calibrated digital scale which will also estimate body composition using bioelectrical impedance.

Height – 2 mins

Height without shoes will be measured to the nearest 0.1cm using a stadiometer.

5 times sit to stand test – 3 mins

Participants sit in a standard straight-backed stable chair (without wheels) positioned by a wall. They then stand fully and sit back down, without using the hands, five times, as quickly as possible.

Post-operative complications

Presence and type of any morbidity. This will be based on medical records for complications during the hospital stay and on participants reporting it using a standard proforma for complications following discharge. They will be graded (as I-V) independently by two researchers blinded to treatment allocation with the Clavien-Dindo classification of post-operative complications, the most widely used and validated measure.[56]

Table 1: Clavien-Dindo classification of post-operative complications

	Morbidity grade definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. Grade I also includes wound infection opened at the bedside.
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Grade II also includes blood transfusions and total parenteral nutrition.
III	Requiring surgical, endoscopic, or radiological intervention.
IIIa	- Not under general anaesthesia
IIIb	- Under general anaesthesia
IV	Life-threatening complication (including central nervous system complications) requiring intensive care unit management
IVa	- Single organ dysfunction
IVb	- Multiorgan dysfunction
V	Death

Adverse events (AEs)

Patient will self-report potential adverse events.

Fitness to discharge

This will be extracted from medical records and be used to calculate the length of hospital stay and, together with survival, the days alive and out of hospital.

Operative outcomes

These will be extracted from medical records.

At discharge:

- *Intraoperative blood loss, in mL*
- *Operative time, in minutes*
- *Conversion to open surgery (yes/no)*

At discharge and 30 days post-operatively:

- *Surgical site infection*
- *Time in intensive care unit and high dependency unit*

At 30 days post-operatively and at 3 years:

- *Re-operation rate*
- Re-admission rate

Descriptive data on the initial operation approach, operation type, and grade of surgeon performing the operation, will also be extracted.

Oncological outcomes

These will be extracted from medical records

At 30 days post-operatively:

- Fitness to receive planned adjuvant therapy

At discharge, 30 days post-operatively, and 3 years:

- *Survival*

At 3 years:

- *Recurrence*
- *New primary/secondary cancer*

Descriptive data on tumour histological staging and lymph node yield, if lymphadenectomy is attempted, will also be extracted.

Feedback questionnaire pre-surgery by intervention participants – 2 mins

This 8-item questionnaire will assess intervention acceptability using adapted questions from the Theoretical Framework of Acceptability questionnaire.[57]

Feedback questionnaire post-surgery – 5 mins

This 11-item study-specific questionnaire will assess satisfaction with trial processes, potential contamination of the usual care group, and satisfaction with the intervention for the intervention participants.

Qualitative interviews with intervention participants – ~45min

Interviews will invite views on (a) the delivery of the programme, (b) barriers to engagement, (c) barriers to adherence, (d) facilitators to adherence while providing flexibility to participants to discuss their views in their own way highlighting aspects of experience that were particularly important to them. They will also capture participants' views on changes in physical activity. The sample size should allow saturation to be reached.[58] Interviews will also cover gastrointestinal symptoms relevant to the intervention (e.g., constipation). The topic guide (Appendix C) may be refined as the study progresses, as per best practice. Interviews will be conducted over the phone/MS Teams, will be audio-recorded, and transcribed verbatim.

Qualitative interviews with research and clinical staff – ~45min

These interviews will aim to explore understanding of trial rationale, design, equipoise, perceptions of the intervention, whether staff would (or not) discuss the trial based on criteria beyond the inclusion/exclusion criteria, concerns, perception of patients' reactions to the trial, recruitment procedures, and relevance of results to their own practice. The topic guide (Appendix D) may be refined as the study progresses, as per best practice. Interviews will be conducted over the phone/MS Teams, will be audio-recorded, and transcribed verbatim.

Fidelity of delivery

A researcher not delivering the intervention will observe a random 10% subsample of the initial dietetic consultations and a 10% subsample of the subsequent dietetic consultations (i.e., join the phone/video call) as they occur and code them with pre-specified criteria to assess fidelity of delivery.

Assessment of screening logs

The local study teams will frequently provide fully anonymised screening logs to the central study team. These logs will be assessed using the SEAR (screening, eligibility, approach, and randomisation) framework for identification of screen failures and dropouts.[59]

9.7. Baseline Assessments

The baseline face-to-face assessment will be conducted during the screening visit at each site. It will last approximately 1.5 hours and it will include:

- Demographic questionnaire
- Concomitant medication
- EQ-5D-5L questionnaire
- HADS questionnaire
- Resource use questionnaire
- Height
- Weight and fat-free mass
- 5 times sit to stand test

9.8. Subsequent Assessments

The study schedule is available in Appendix B. The window periods will be:

- 7 days for the pre-operative follow-up assessment 1 (3 days before the time the interview is expected to occur to 3 days after that)
- 4 days for the pre-operative follow-up assessment 2 (From the day of the assessment is expected to occur (4 days pre-operatively) to the day of surgery
- Between admission and surgery for the pre-operative follow-up assessment 3
- 27-37 days post-operative for the post-operative follow-up assessment scheduled 30 days post-operative
- 3-year follow-up from medical records: 3 years ± 6 months post-operatively

Pre-operative follow-up assessment 1 – only for participants in the intervention group

Qualitative interviews with intervention participants. Interviews will occur approximately halfway through the programme, so that participants are well into the intervention but not too close to surgery to better capture the whole pre-operative experience.

Pre-operative follow-up assessment 2 – all participants

This will include the EQ-5D-5L and HADS questionnaires for all participants. In addition, it will include the feedback pre-surgery questionnaire for intervention participants only. Participants will choose to receive either a link to fill in the questionnaires electronically or a paper questionnaire that they can post or bring in clinic on the day of surgery. Participants will receive email and/or phone reminders to facilitate questionnaire completion

Pre-operative follow-up assessment 3 – all participants

This will include weight and fat-free mass.

Post-operative follow-up assessment – all participants

Where possible, this face-to-face assessment will occur jointly with the standard clinical follow-up appointment to minimise travel. It will include:

- Post-operative complications reporting
- EQ-5D-5L questionnaire
- EORTC-QLQ-EN24 questionnaire (only completed post-operatively as many questions are not relevant pre-operatively)
- HADS questionnaire
- Resource use questionnaire
- Weight and fat-free mass
- 5 times sit to stand test
- Adverse events
- Post-surgery feedback questionnaire

Staff assessment

A purposive subsample of research and clinical staff (around 16) will be invited for a 45-minute qualitative interview. This includes any research and clinical staff involved in the study and recruitment process. A member of the central research team will email local staff inviting them to take part in the study. Staff will be given an information sheet and provide informed consent prior to interview.

Long-term follow-up through the hospital medical records

We will extract relevant data collected as part of routine care at each study site for up to 3 years after each participant completes the study. The type and timing of relevant data collected will depend on data availability based on each participant's routine clinical care. This is likely to include weight, morbidity, mortality, disease progression, new diagnoses, medication, re-admission, re-operation, and healthcare resource use.

9.9. Sample Handling

No samples will be taken.

9.10. Early Discontinuation/Withdrawal of Participants

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

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

Participants in the care as usual group: They may opt out of study assessments but may remain on study follow-up.

Participants in the intervention group: They may stop the intervention and/or study assessments but may remain on study follow-up and will be encouraged to do so.

All participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. In the case of withdrawal from both treatment (i.e., intervention) and active follow up, the following options for a tiered withdrawal from the study will be given to participants and explained in the participant information sheet.

According to the design of the study, option 1 below will be the default. Alternatively, participants can explicitly opt for option 2.

1) Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.

2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

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

- Participant declining surgery
- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-adherence with the intervention or trial requirements
- Clinical decision

The follow-up of participants that have withdrawn from the intervention but not from active follow-up will continue with the standard follow-up assessments of the study.

Data from randomised participants who undergo curative surgery for endometrial cancer will be analysed. Post-randomisation withdrawal from the study will not result in exclusion of the data for that participant from the analysis. However, participants will be replaced as per section 9.3 if

- they have been randomised but have not undergone curative surgery for endometrial cancer
- they have been randomised but deemed ineligible during the study or retrospectively

or

- they have withdrawn before randomisation.

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

If the participant is withdrawn due to an AE, the investigator will arrange for frequent telephone calls as agreed with the participant until the AE has resolved or stabilised (also see sections 9.6.4 and 10) and up to the point the participant completes the study. If a participant is withdrawn from treatment due to pregnancy the pregnancy will be followed-up to outcome. See the Safety Reporting section below.

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

9.11. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved. This includes the long-term follow-up.

10. SAFETY REPORTING

Potential AEs will be recorded at pre-operative follow-up assessment 1 and the post-operative assessment. Participants may contact the research team (e.g., over the phone) at any time point during the course of the study to report potential AEs. AEs will be recorded as part of the eCRF of the subsequent assessment (e.g., an AE occurring between pre-operative assessment 1 and 2 will be recorded as part of the pre-operative assessment 2.

One previous trial reported no SAEs due to the TDR, whereas another reported two SAEs potentially related to the TDR in the same participant.[16, 17] There was evidence that for every five people one would experience an adverse, mostly mild, event because of the TDR programme.[16] Constipation, headache, fatigue, and dizziness are the most common AEs albeit occurring in a minority of participants (<8% each) and disappeared over time.[16, 17] Less common side effects include dry mouth, abdominal pain, bad breath, diarrhoea, hair loss, dry skin, mood changes, and feeling cold.

The safety reporting window begins from the first day of the intervention for participants in the intervention group and from the day of randomisation for participants in the control group. It finishes for both groups when the participant completes the study. The limit of investigator follow-up of SAEs will be until the participant completes the study. This requirement will be the same for all SAEs.

Operative and post-operative complications or the responses to questionnaires (e.g., change in anxiety levels) will not be reported as AEs, as they will be extracted as part of the study outcomes.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

- consists of a congenital anomaly or birth defect.

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

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). The Trial Steering Committee (TSC) may advise reporting to REC if the frequency of deaths is significantly higher than that expected in this population. As per 10, operative and post-operative complications that could meet the definition of SAEs will not be reported as SAEs, as they will be reported as part of the study outcomes, but the TSC will monitor the frequency of complications and may advise reporting at their discretion.

11. STATISTICS AND ANALYSIS

A Statistical Analysis Plan (SAP) is to be produced separately.

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a SAP that will be written and finalised before the time that the first participant is recruited. The SAP will be reviewed prior to final database lock, and, if an amendment is deemed necessary, then this will be documented.

11.2. Description of the Statistical Methods

A table will present the baseline demographic and clinical characteristics. Continuous variables will be summarised using means, standard deviations, and 95% confidence intervals. Medians with interquartile ranges will be presented where appropriate. Categorical variables will be summarised using counts and percentages. Exploratory between-group comparisons will be reported where appropriate. Data will be analysed using appropriate statistical software.

Progression criteria (as defined in Table 2) will be summarised descriptively for all participants [and by trial group, trial site, and neoadjuvant treatment (yes/no) as appropriate]. Uncertainty in the progression criteria will be expressed with 95% confidence intervals.

Table 2: Progression criteria

Sufficient levels of		Criterion Decision	**Green** **Progress**	**Amber** **Progress with changes**		**Red** **Stop**
Recruitment	1a	Rate (n of patients per site per month)	≥0.75	0.46-0.74	Progress by adding sites.	≤0.45
	1b	Number of sites open	≥6 sites	3-5		≤2
	1c	Total N participants recruited	72	44-71		≤43
Engagement	2	Proportion of phone calls answered	≥75%	51-74%	Progress if process evaluation can recommend improvements.	≤50%
Adherence	3	Proportion of intervention participants with ≥5% weight loss from baseline to the day of surgery[2]	≥60%	36-59%		≤35%
Retention	4	% at final follow-up	≥85%	66-84%		≤65%
Safety	5	Safety profile	Based on adverse and serious adverse reactions. Adjudicated by the Data Monitoring and Ethics Committee.			

[1] **Adherence:** Non-adherence will be defined as <2% weight loss from baseline to the day of surgery. Participants will also rate in their weekly phone call their adherence to the intervention on a 0-100 scale.

All other outcomes will be summarised descriptively by trial arm. Where appropriate, the effect size and 95% confidence intervals will be estimated with regression models adjusting for treatment group, baseline value (where applicable), and stratification variables. Both absolute and relative effect sizes will be reported. No subgroup analyses are planned.

Complications will be summarised using:

- count/percentage of participants with any complication
- count/percentage of participants with any complication by grade
- count/percentage of participants with the highest grade of complication reported
- count/percentage of participants with any type of complication
- count of total complications.

11.3. Sample Size Determination

With 72 patients (n=36 per arm), the trial will be 90% powered at one-sided 5% level based on the normal approximation approach to detect whether the proportions for the engagement, adherence, and retention criteria in Table 2 are truly above the upper limit of the red zone (>50% engagement, >35% adherence, >65% follow-up) based on an alternative being in the green zone.[60] The collective power for all three criteria is 85% at 5% level, without multiple testing adjustment. Recalculating the sample size on a binomial approach (sensitivity analysis) provided almost identical estimates.[60]

A purposive subsample of research and clinical staff (around 16) will be invited for a 45-minute qualitative interview. This includes any research and clinical staff involved in the study and recruitment

process. This sample size will aim to capture views from research and clinical staff from sites with both high and low recruitment rates and from a variety of roles and levels of experience (e.g., consultants, registrars, research nurses, research practitioners). The exact sample size will depend on reaching information redundancy.

11.4. Analysis populations

All randomised and eligible participants that underwent surgery will be included in the main analysis on an intention-to-treat principle regardless of withdrawal or non-adherence. A per protocol analysis will include the subsample of intervention participants who achieved ≥5% weight loss from baseline to the day of surgery. The adverse event analysis will include the participants in the control group and the participants commencing the intervention in the intervention group.

11.5. Decision points

No interim analysis is planned.

11.6. Stopping rules

The TSC may formally recommend early termination if needed in line with the TSC charter.

11.7. The Level of Statistical Significance

P-values will not be reported given the feasibility nature of the trial.[61] There will be no adjustment for multiple testing.[62] The 95% confidence intervals will be presented but regarded nominal and descriptive.

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

Missing data will be imputed using appropriate methodology, as detailed in the SAP.

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

Deviations from the original SAP will be reported and justified at publication following the CONSORT guidelines.

11.10. Qualitative Analysis

Qualitative data will be transcribed verbatim, de-identified, and analysed in NVivo.

Analysis of qualitative interviews with intervention participants and staff: Data will be analysed using thematic analysis while data collection is ongoing.[63] This will aim to identify themes at an explicit level using a realist approach. A second coder will re-code a random 10% sub-sample to validate the coding.

11.11. Health Economic analysis

Data on health economic aspects (intervention costs, healthcare resource use, and quality-adjusted life years) will be collected (see 9.6.4) and described to allow for planning of the health economics analysis in a future definitive trial.

Intervention costs will include training for intervention delivery, intervention delivery, administrative time, and meal replacement products.

Healthcare resource use will be quantified base on self-reported questions as per 9.6.3 and hospital records. The hospital records will be used to quantify secondary care resource use, as it is anticipated that all secondary care for each patient will be received at the recruitment hospital. Secondary care resource use will include complications, fitness to discharge, operative outcomes, and oncological outcomes as per 9.6.3. Healthcare resource use will be valued using unit costs from UK NHS reference costs and the most recent Personal Social Services Research Unit.

Quality-adjusted life years will be estimated based on the collected EQ-5D-5L data using UK utility values.

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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

Audio recordings will be collected using an encrypted audio-recorder (or recorded via an alternative Sponsor-approved secure device/mechanism).

12.2. Access to Data

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

Names and contact details (address and phone number) of participants receiving the intervention will be shared with the company providing the meal replacement products and the delivery company for the sole purpose of selecting and delivering the products to the participants. Participants will also be informed that their audio recordings are transferred to a professional transcription company for transcription purposes. These transfers will be through an appropriately secure communications procedure in line with the University of Oxford's Information Security Handling Rules.

12.3. Data Recording and Record Keeping

This study will be run using the Surgical Intervention Trials Unit standard operating procedures (SOPs) for guidance.

All trial data, except the audio recording files, will be entered on REDCap, which will host the eCRF. The validation process with be in line with the SOPs and include naming variables, eCRF design, data verification and validation (range and logic tests), test data entry, and data export verification. Each site will be provided with a tablet, so that participants can consent and directly answer questionnaires during study visits on REDCap rather than paper-based copies.

Identifiable, personal data will be retained centrally on REDCap (i.e. by the sponsoring organisation). The participants will be identified by a unique trial specific number and/or code in any database for analysis outside REDCap (i.e., they will be excluded from any data exports for data analysis). Research documents with personal information, such as consent forms, will be held securely at the University of Oxford until the end of the study. They will then be securely deleted.

Following review to ensure participant anonymity is safeguarded and subject to any reasonable and necessary delay, de-identified research data will be securely archived to a repository following publication of the results where they will be stored indefinitely. These data may be used in future research, here or abroad, and may involve commercial organisations.

In line with the departmental Data Transfer Policy, transfer of the audio recordings from the University to University-approved transcription companies will be done securely through the University-approved Nexus365 OneDrive or equivalent. The audio recording files will be securely stored in OneDrive. Copies held by the transcription company will be deleted following receipt of the pseudonymised transcript by the University (i.e., through upload to OneDrive or equivalent). This will follow the departmental Data Transfer Policy. The audio recordings will be linked to the rest of the data using the unique trial specific ID number in the file name. The copy of the audio recordings held at the University will be retained until completion of relevant analysis and they will then be securely deleted. The de-identified transcripts will be retained in line with the rest of the de-identified research data.

Prior to database lock, the database will be reviewed to ensure all queries have been resolved and the dataset is complete.

The Data Management will be compliant with the University of Oxford's policy (https://researchsupport.admin.ox.ac.uk/policy/data).

13. QUALITY ASSURANCE PROCEDURES

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

13.1. Risk assessment

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

13.2. Study monitoring

Regular monitoring will be performed according the Surgical Intervention Trials Unit SOPs. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Data will be monitored for quality and completeness by the Surgical Intervention Trials Unit, using established verification, validation and checking processes. Missing data will be chased until they are received, confirmed as not available, or when the trial is at analysis. Reminders will be sent to participants if questionnaires are not completed within a specified period (section 9), and researchers will also contact participants by telephone to facilitate data completion where appropriate.

The Surgical Intervention Trials Unit/Sponsor reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the Surgical Intervention Trials Unit/Sponsor. Source data verification will involve direct access to patient notes at the participating NHS Sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

Following written SOPs, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.3. Study Committees

13.3.1 Trial Management Committee

The trial management committee will comprise of all named investigators, the trial manager, relevant staff from the Surgical Intervention Trials Unit, patient and public involvement representatives, and other key personnel involved in the trial. It will be responsible for the design of the trial and the day-to-day management in line with the committee's Charter. The Committee will initially meet monthly and the frequency of the meetings will be adjusted depending on progress.

13.3.2 Independent Trial Steering Committee

As this is an unblinded trial (with blinded outcome assessment), a separate Data Monitoring and Ethics Committee is not required. The TSC will also assume the role of the Data Monitoring and Ethics Committee. It will comprise of an independent Chair (academic endometrial surgeon), an independent academic, independent statistician, a patient and public representative.

14. PROTOCOL DEVIATIONS

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

The Surgical Intervention Trials Unit's SOPs will be followed for identifying non-compliances, escalation to the central team, and assessment of whether a non-compliance/deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

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

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

(b) the scientific value of the research.

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

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

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

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

16.4. Other Ethical Considerations

Clinical equipoise

There is some promising evidence that weight loss improves outcomes following other types of surgery, but there is a lack of evidence on whether intentional weight loss improves recovery following endometrial cancer surgery. This leads to clinical equipoise of whether this treatment should be offered and justifies the need for randomisation. Additionally, whether the definitive trial is feasible remains unclear justifying the need for this feasibility trial.

Adverse events

AEs during the intervention period have previously shown to be infrequent and disappear over time (see section 10). The dietitian will support the participants during the frequent consultations in managing potential AEs based on current clinical guidance. The research team will handle the AEs when reported in a sensitive manner and in line with section 10.

16.5. Reporting

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

16.6. Transparency in Research

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

The trial information will be kept up to date during the trial, and the CI or their delegate will upload results within 12 months of the end of the trial declaration.

16.7. Participant Confidentiality

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

16.8. Expenses and Benefits

We will offer participants a voucher following the baseline assessment and another voucher of the same value following the post-operative follow-up assessment as compensation for reasonable travel expenses occurred to attend study visits. The value of the voucher will be £15 or £30 and will depend on the length of travel and from the hospital. This approach will allow us to compensate participants more fairly than a voucher of a single value.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the NIHR (Grant Reference Number NIHR302549).

17.2. Insurance

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

17.3. Contractual arrangements

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

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health and Care Research (NIHR). The views expressed will be those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

19. ARCHIVING

This will be in line with section 12.3. De-identified data will be indefinitely archived in a repository. Identifiable data will not be archived (i.e., they will be deleted at the end of the study).

20. REFERENCES

- [1] K. Bhaskaran, I. Douglas, H. Forbes, I. dos-Santos-Silva, D.A. Leon, L. Smeeth, Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults, Lancet 384(9945) (2014) 755-65.
- [2] F. Bouwman, A. Smits, A. Lopes, N. Das, A. Pollard, L. Massuger, R. Bekkers, K. Galaal, The impact of BMI on surgical complications and outcomes in endometrial cancer surgery--an institutional study and systematic review of the literature, Gynecologic oncology 139(2) (2015) 369-76.
- [3] O. Orekoya, M.E. Samson, T. Trivedi, S. Vyas, S.E. Steck, The Impact of Obesity on Surgical Outcome in Endometrial Cancer Patients: A Systematic Review, J Gynecol Surg 32(3) (2016) 149-157.
- [4] E.J. Crosbie, C. Roberts, W. Qian, A.M. Swart, H.C. Kitchener, A.G. Renehan, Body mass index does not influence post-treatment survival in early stage endometrial cancer: results from the MRC ASTEC trial, European journal of cancer 48(6) (2012) 853-64.
- [5] A. Weimann, M. Braga, F. Carli, T. Higashiguchi, M. Hubner, S. Klek, A. Laviano, O. Ljungqvist, D.N. Lobo, R. Martindale, D.L. Waitzberg, S.C. Bischoff, P. Singer, ESPEN guideline: Clinical nutrition in surgery, Clin Nutr 36(3) (2017) 623-650.
- [6] Macmillan, Prehabilitation evidence and insight review, 2017. https://www.macmillan.org.uk/_images/prehabilitation-evidence-and-insight-review_tcm9-335025.pdf. (Accessed 2 November 2021.
- [7] O. Boney, M. Bell, N. Bell, A. Conquest, M. Cumbers, S. Drake, M. Galsworthy, J. Gath, M.P. Grocott, E. Harris, S. Howell, A. Ingold, M.H. Nathanson, T. Pinkney, L. Metcalf, Identifying research priorities in anaesthesia and perioperative care: final report of the joint National Institute of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partnership, BMJ Open 5(12) (2015) e010006.
- [8] JLA, Living With and Beyond Cancer Top 10, 2018. https://www.jla.nihr.ac.uk/priority-setting-partnerships/living-with-and-beyond-cancer/top-10-priorities.htm. (Accessed 27 Sept 2021.
- [9] D.T. Villareal, S. Chode, N. Parimi, D.R. Sinacore, T. Hilton, R. Armamento-Villareal, N. Napoli, C. Qualls, K. Shah, Weight loss, exercise, or both and physical function in obese older adults, N Engl J Med 364(13) (2011) 1218-29.

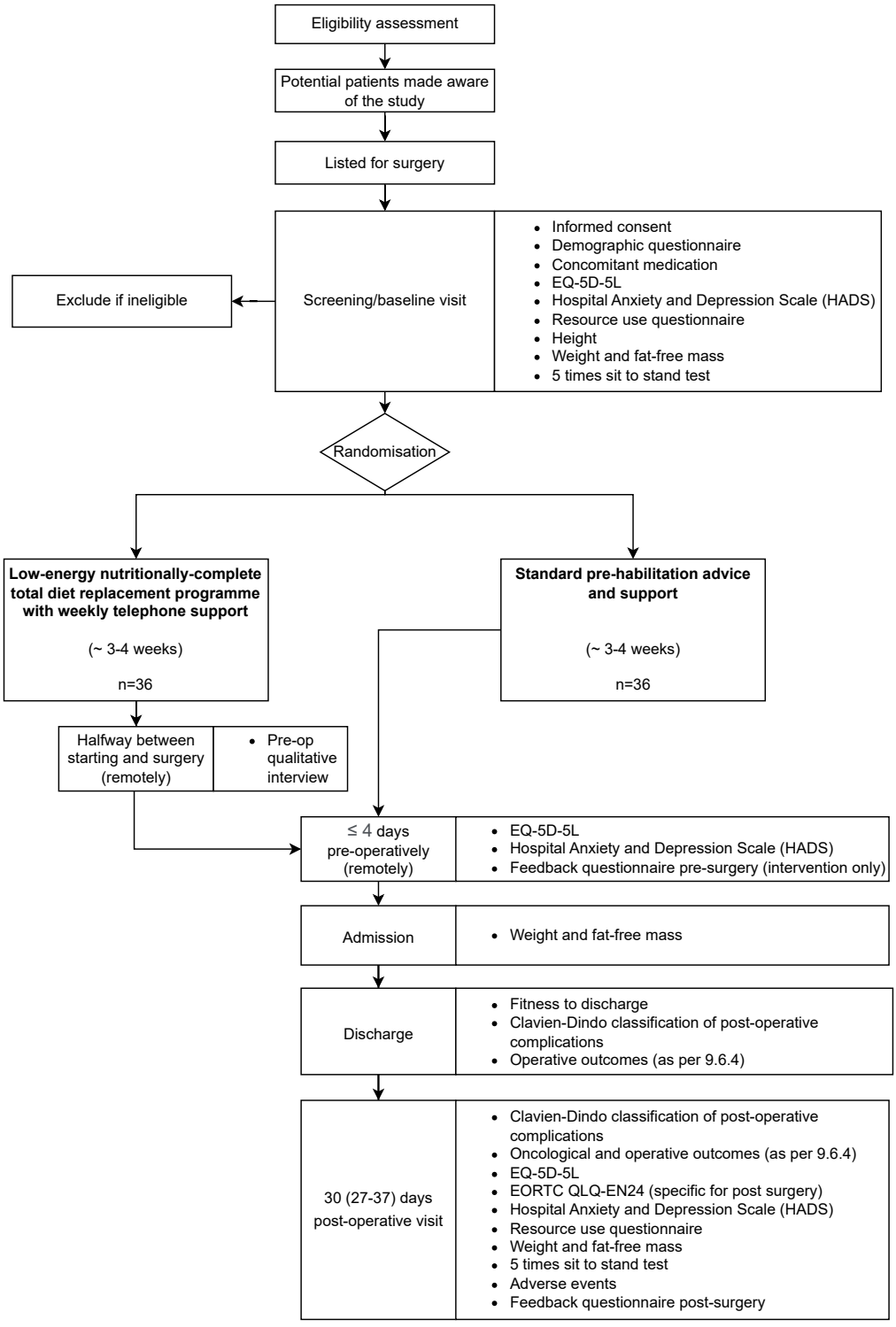
- [10] C.P. Snowden, J. Prentis, B. Jacques, H. Anderson, D. Manas, D. Jones, M. Trenell, Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people, Annals of surgery 257(6) (2013) 999-1004.
- [11] A. Heldens, B.C. Bongers, A.F. Lenssen, L.P.S. Stassen, W.F. Buhre, N.L.U. van Meeteren, The association between performance parameters of physical fitness and postoperative outcomes in patients undergoing colorectal surgery: An evaluation of care data, Eur J Surg Oncol 43(11) (2017) 2084-2092.
- [12] M. Kotagal, R.G. Symons, I.B. Hirsch, G.E. Umpierrez, E.P. Dellinger, E.T. Farrokhi, D.R. Flum, S.-C. Collaborative, Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes, Annals of surgery 261(1) (2015) 97-103.
- [13] E. Selvin, N.P. Paynter, T.P. Erlinger, The effect of weight loss on C-reactive protein: a systematic review, Arch Intern Med 167(1) (2007) 31-9.
- [14] J.H. Park, D.G. Watt, C.S. Roxburgh, P.G. Horgan, D.C. McMillan, Colorectal Cancer, Systemic Inflammation, and Outcome: Staging the Tumor and Staging the Host, Annals of surgery 263(2) (2016) 326-36.
- [15] Y. Sun, B. Liu, J.K. Smith, M.L.G. Correia, D.L. Jones, Z. Zhu, A. Taiwo, L.L. Morselli, K. Robinson, A.A. Hart, L.G. Snetselaar, W. Bao, Association of Preoperative Body Weight and Weight Loss With Risk of Death After Bariatric Surgery, JAMA Netw Open 3(5) (2020) e204803.
- [16] N.M. Astbury, P. Aveyard, A. Nickless, K. Hood, K. Corfield, R. Lowe, S.A. Jebb, Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial, BMJ 362 (2018) k3760.
- [17] M.E. Lean, W.S. Leslie, A.C. Barnes, N. Brosnahan, G. Thom, L. McCombie, C. Peters, S. Zhyzhneuskaya, A. Al-Mrabeh, K.G. Hollingsworth, A.M. Rodrigues, L. Rehackova, A.J. Adamson, F.F. Sniehotta, J.C. Mathers, H.M. Ross, Y. McIlvenna, R. Stefanetti, M. Trenell, P. Welsh, S. Kean, I. Ford, A. McConnachie, N. Sattar, R. Taylor, Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial, Lancet 391(10120) (2018) 541-551.
- [18] R.V. Seimon, A.L. Wild-Taylor, S.E. Keating, S. McClintock, C. Harper, A.A. Gibson, N.A. Johnson, H.A. Fernando, T.P. Markovic, J.R. Center, J. Franklin, P.Y. Liu, S.M. Grieve, J. Lagopoulos, I.D. Caterson, N.M. Byrne, A. Sainsbury, Effect of Weight Loss via Severe vs Moderate Energy Restriction on Lean Mass and Body Composition Among Postmenopausal Women With Obesity: The TEMPO Diet Randomized Clinical Trial, JAMA Netw Open 2(10) (2019) e1913733.
- [19] S. Taheri, H. Zaghloul, O. Chagoury, S. Elhadad, S.H. Ahmed, N. El Khatib, R.A. Amona, K. El Nahas, N. Suleiman, A. Alnaama, A. Al-Hamaq, M. Charlson, M.T. Wells, S. Al-Abdulla, A.B. Abou-Samra, Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial, Lancet Diabetes Endocrinol 8(6) (2020) 477-489.
- [20] J.D. Ard, K.H. Lewis, A. Rothberg, A. Auriemma, S.L. Coburn, S.S. Cohen, J. Loper, L. Matarese, W.J. Pories, S. Periman, Effectiveness of a Total Meal Replacement Program (OPTIFAST Program) on Weight Loss: Results from the OPTIWIN Study, Obesity (Silver Spring) 27(1) (2019) 22-29.
- [21] D.A. Koutoukidis, F. Mozes, S.A. Jebb, J.W. Tomlinson, M. Pavlides, F. Saffioti, R. Huntriss, P. Aveyard, J.F. Cobbold, A low-energy total diet replacement programme demonstrates a favourable safety profile and improves liver disease severity in non-alcoholic steatohepatitis, Obesity (Silver Spring) In press.
- [22] S.A.L. Price, P. Sumithran, A.J. Nankervis, M. Permezel, L.A. Prendergast, J. Proietto, Impact of preconception weight loss on fasting glucose and pregnancy outcomes in women with obesity: A randomized trial, Obesity (Silver Spring) 29(9) (2021) 1445-1457.
- [23] P. Christensen, M. Henriksen, E.M. Bartels, A.R. Leeds, T. Meinert Larsen, H. Gudbergsen, B.F. Riecke, A. Astrup, B.L. Heitmann, M. Boesen, R. Christensen, H. Bliddal, Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial, Am J Clin Nutr 106(3) (2017) 755-763.

- [24] C.J. Haywood, L.A. Prendergast, K. Purcell, L. Le Fevre, W.K. Lim, M. Galea, J. Proietto, Very Low Calorie Diets for Weight Loss in Obese Older Adults-A Randomized Trial, J Gerontol A Biol Sci Med Sci 73(1) (2017) 59-65.
- [25] R. Wijesurendra, M. Spartera, S. Neubauer, S.A. Jebb, D.A. Koutoukidis, P. Aveyard, C. Antoniades, J. Smith, B. Casadei, Weight Loss in Elderly Patients with Atrial Fibrillation (LOSE-AF): A Randomised Controlled Trial, Preliminary results.
- [26] NHS, Low calorie diets to treat obesity and Type 2 diabetes, 2020. https://www.england.nhs.uk/diabetes/treatment-care/low-calorie-diets/. (Accessed 15 October 2021.
- [27] N.M. Astbury, K. Tudor, P. Aveyard, S.A. Jebb, Heterogeneity in the uptake, attendance, and outcomes in a clinical trial of a total diet replacement weight loss programme, BMC Med 18(1) (2020) 86.
- [28] A. Downing, E.J. Morris, M. Richards, J. Corner, P. Wright, D. Sebag-Montefiore, P. Finan, P. Kind, C. Wood, S. Lawton, R. Feltbower, R. Wagland, S. Vernon, J. Thomas, A.W. Glaser, Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis, Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(6) (2015) 616-24.
- [29] J.S. Abelson, A. Chait, M.J. Shen, M. Charlson, A. Dickerman, H.L. Yeo, Sources of distress among patients undergoing surgery for colorectal cancer: a qualitative study, J Surg Res 226 (2018) 140-149.
- [30] A. Beck, H.V. Thaysen, C.H. Soegaard, J. Blaakaer, L. Seibaek, Investigating the experiences, thoughts, and feelings underlying and influencing prehabilitation among cancer patients: a qualitative perspective on the what, when, where, who, and why, Disability and rehabilitation (2020) 1-8.
- [31] N.M. Astbury, C. Albury, R. Nourse, S.A. Jebb, Participant experiences of a low-energy total diet replacement programme: A descriptive qualitative study, PLoS One 15(9) (2020) e0238645.
- [32] S.M. Bluethmann, K. Basen-Engquist, S.W. Vernon, M. Cox, K.P. Gabriel, S.A. Stansberry, C.L. Carmack, J.A. Blalock, W. Demark-Wahnefried, Grasping the 'teachable moment': time since diagnosis, symptom burden and health behaviors in breast, colorectal and prostate cancer survivors, Psycho-oncology 24(10) (2015) 1250-1257.
- [33] R.J. Beeken, K. Williams, J. Wardle, H. Croker, "What about diet?" A qualitative study of cancer survivors' views on diet and cancer and their sources of information, European journal of cancer care 25(5) (2016) 774-83.
- [34] M. van Zutphen, H.C. Boshuizen, D.E. Kok, H. van Baar, A. Geijsen, E. Wesselink, R.M. Winkels, H.K. van Halteren, J.H.W. de Wilt, E. Kampman, F.J.B. van Duijnhoven, Colorectal cancer survivors only marginally change their overall lifestyle in the first 2 years following diagnosis, Journal of cancer survivorship : research and practice 13(6) (2019) 956-967.
- [35] W. Demark-Wahnefried, L.Q. Rogers, J.T. Gibson, S. Harada, A.D. Fruge, R.A. Oster, W.E. Grizzle, L.A. Norian, E.S. Yang, D. Della Manna, L.W. Jones, M. Azrad, H. Krontiras, Randomized trial of weight loss in primary breast cancer: Impact on body composition, circulating biomarkers and tumor characteristics, International journal of cancer. Journal international du cancer 146(10) (2020) 2784-2796.
- [36] W. Demark-Wahnefried, J.W. Nix, G.R. Hunter, S. Rais-Bahrami, R.A. Desmond, B. Chacko, C.D. Morrow, M. Azrad, A.D. Fruge, Y. Tsuruta, T. Ptacek, S.A. Tully, R. Segal, W.E. Grizzle, Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer, BMC cancer 16 (2016) 61.
- [37] A.D. Fruge, J.A. Dasher, D. Bryan, S. Rais-Bahrami, W. Demark-Wahnefried, G.R. Hunter, Physiological Effort in Submaximal Fitness Tests Predicts Weight Loss in Overweight and Obese Men with Prostate Cancer in a Weight Loss Trial, Int J Cancer Clin Res 4(2) (2017).
- [38] K. Inoue, S. Yoshiuchi, M. Yoshida, N. Nakamura, S. Nakajima, A. Kitamura, K. Mouri, T. Michiura, H. Mukaide, T. Ozaki, H. Miki, H. Yanagimoto, S. Satoi, M. Kaibori, M. Hamada, Y. Kimura, M. Kon, Preoperative weight loss program involving a 20-day very low-calorie diet for obesity before laparoscopic gastrectomy for gastric cancer, Asian J Endosc Surg 12(1) (2019) 43-50.

- [39] S. Temraz, H. Tamim, A. Mailhac, F. Nassar, N. Moukalled, F. Jamali, A. Taher, Could Preoperative Unintended Weight Loss Predispose to Postoperative Thrombosis in Patients Undergoing Colorectal Cancer Surgery? An Analysis of the NSQIP Data, J Am Coll Nutr 40(2) (2021) 141-147.
- [40] J. Xiao, B.J. Caan, E.M. Cespedes Feliciano, J.A. Meyerhardt, C.H. Kroenke, V.E. Baracos, E. Weltzien, M.L. Kwan, S.E. Alexeeff, A.L. Castillo, C.M. Prado, The association of medical and demographic characteristics with sarcopenia and low muscle radiodensity in patients with nonmetastatic colorectal cancer, Am J Clin Nutr 109(3) (2019) 615-625.
- [41] E. Cava, N.C. Yeat, B. Mittendorfer, Preserving Healthy Muscle during Weight Loss, Adv Nutr 8(3) (2017) 511-519.
- [42] A. Bosy-Westphal, E. Kossel, K. Goele, W. Later, B. Hitze, U. Settler, M. Heller, C.C. Gluer, S.B. Heymsfield, M.J. Muller, Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure, Am J Clin Nutr 90(4) (2009) 993-1001.
- [43] K.M. Beavers, M.E. Miller, W.J. Rejeski, B.J. Nicklas, S.B. Kritchevsky, Fat mass loss predicts gain in physical function with intentional weight loss in older adults, J Gerontol A Biol Sci Med Sci 68(1) (2013) 80-6.
- [44] H.C. Felix, D.S. West, Effectiveness of weight loss interventions for obese older adults, American journal of health promotion : AJHP 27(3) (2013) 191-9.
- [45] D.W. Kitzman, P. Brubaker, T. Morgan, M. Haykowsky, G. Hundley, W.E. Kraus, J. Eggebeen, B.J. Nicklas, Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial, JAMA 315(1) (2016) 36-46.
- [46] P. Christensen, R. Frederiksen, H. Bliddal, B.F. Riecke, E.M. Bartels, M. Henriksen, S.R.T. Juul, H. Gudbergsen, K. Winther, A. Astrup, R. Christensen, Comparison of three weight maintenance programs on cardiovascular risk, bone and vitamins in sedentary older adults, Obesity (Silver Spring) 21(10) (2013) 1982-90.
- [47] P.G. Vaughan-Shaw, L. Zgaga, L.Y. Ooi, E. Theodoratou, M. Timofeeva, V. Svinti, M. Walker, F. O'Sullivan, A. Ewing, S. Johnston, F.V.N. Din, H. Campbell, S.M. Farrington, M.G. Dunlop, Low plasma vitamin D is associated with adverse colorectal cancer survival after surgical resection, independent of systemic inflammatory response, Gut 69(1) (2020) 103-111.
- [48] M.A. Guinter, M.L. McCullough, S.M. Gapstur, P.T. Campbell, Associations of Pre- and Postdiagnosis Diet Quality With Risk of Mortality Among Men and Women With Colorectal Cancer, Journal of clinical oncology : official journal of the American Society of Clinical Oncology (2018) JCO1800714.
- [49] S. Kent, P. Aveyard, N. Astbury, B. Mihaylova, S.A. Jebb, Is Doctor Referral to a Low-Energy Total Diet Replacement Program Cost-Effective for the Routine Treatment of Obesity?, Obesity (Silver Spring) 27(3) (2019) 391-398.
- [50] Y. Xin, A. Davies, L. McCombie, A. Briggs, C.M. Messow, E. Grieve, W.S. Leslie, R. Taylor, M.E.J. Lean, Within-trial cost and 1-year cost-effectiveness of the DiRECT/Counterweight-Plus weight-management programme to achieve remission of type 2 diabetes, Lancet Diabetes Endocrinol 7(3) (2019) 169-172.
- [51] N.a.A.N. EFSA Panel on Dietetic Products, Scientific Opinion on the essential composition of total diet replacements for weight control, EFSA Journal 13 (2015) 3957.
- [52] C. Harper, J. Maher, A. Grunseit, R.V. Seimon, A. Sainsbury, Experiences of using very low energy diets for weight loss by people with overweight or obesity: a review of qualitative research, Obesity reviews : an official journal of the International Association for the Study of Obesity 19(10) (2018) 1412-1423.
- [53] NHS, National Cancer Waiting Times Monitoring Dataset v12, 2022. https://www.england.nhs.uk/wp-content/uploads/2022/03/B1368-national-cancer-waiting-times-monitoring-dataset-guidance-version-12..0-march-2022-2.pdf. (Accessed 27 October 2022.

- [54] P.-A.T. Collaborative, SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery trial (PREPARE-ABC): Pilot phase of a multicentre randomised controlled trial, Colorectal Dis (2021).
- [55] PSSRU, Client Service Receipt Inventory (CSRI), 2022. https://www.pssru.ac.uk/csri/client-service-receipt-inventory/. (Accessed 14 August 2022.
- [56] P.A. Clavien, J. Barkun, M.L. de Oliveira, J.N. Vauthey, D. Dindo, R.D. Schulick, E. de Santibanes, J. Pekolj, K. Slankamenac, C. Bassi, R. Graf, R. Vonlanthen, R. Padbury, J.L. Cameron, M. Makuuchi, The Clavien-Dindo classification of surgical complications: five-year experience, Annals of surgery 250(2) (2009) 187-96.
- [57] M. Sekhon, M. Cartwright, J.J. Francis, Development of a theory-informed questionnaire to assess the acceptability of healthcare interventions, BMC health services research 22(1) (2022) 279.
- [58] G. Guest, A. Bunce, L. Johnson, How Many Interviews Are Enough?:An Experiment with Data Saturation and Variability, Field Methods 18(1) (2006) 59-82.
- [59] C. Wilson, L. Rooshenas, S. Paramasivan, D. Elliott, M. Jepson, S. Strong, A. Birtle, D.J. Beard, A. Halliday, F.C. Hamdy, R. Lewis, C. Metcalfe, C.A. Rogers, R.C. Stein, J.M. Blazeby, J.L. Donovan, Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework, Trials 19(1) (2018) 50.
- [60] M. Lewis, K. Bromley, C.J. Sutton, G. McCray, H.L. Myers, G.A. Lancaster, Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back!, Pilot Feasibility Stud 7(1) (2021) 40.
- [61] S.M. Eldridge, C.L. Chan, M.J. Campbell, C.M. Bond, S. Hopewell, L. Thabane, G.A. Lancaster, P.c. group, CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Pilot Feasibility Stud 2 (2016) 64.
- [62] G. Li, M. Taljaard, E.R. Van den Heuvel, M.A. Levine, D.J. Cook, G.A. Wells, P.J. Devereaux, L. Thabane, An introduction to multiplicity issues in clinical trials: the what, why, when and how, Int J Epidemiol 46(2) (2017) 746-755.
- [63] V. Braun, V. Clarke, Using thematic analysis in psychology, Qualit Res Psychol 3 (2006) 77-101.

21. APPENDIX A: STUDY FLOW CHART



Throughout: qualitative interviews with clinical and research staff

22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

	Assessments							
	From suspicion of cancer to diagnosis	From diagnosis to 3 d post diagnosis	Halfway from starting intervention to surgery (± 3 d)	4 d pre-op to day of surgery	Admission	Discharge (~5-7 days post-op)	30 d post-op (27-37 d)	3y (± 6m) post-op
Procedures	**Pre-screening**	**Screening / baseline**	**Pre-op 1**	**Pre-op 2**	**Pre-op 3**	**Discharge**	**Post-op**	**Long-term follow-up**
Informed consent		X						
Eligibility assessment	X	X						
Demographic q		X						
Concomitant medication		X						
Randomisation		X						
EQ-5D-5L q		X		X			X	
EORTC-QLQ-EN24 q							X	
HADS q		X		X			X	
Resource use q		X					X	
Pre-op qualitative interview*			X					
Feedback q pre-surgery*				X				
Feedback q post-surgery							X	
Height		X						
Weight & fat-free mass		X			X		X	
5 times sit to stand test		X					X	
Fitness of discharge assessment						X		
Complications (Clavien-Dindo)						X	X	
Operative outcomes						X	X	X
Oncological outcomes							X	X
Fidelity of intervention delivery			←	→				
Record AEs, as applicable			←	→	→	→	X	
Qualitative interviews with staff	Throughout the trial							
Assessments of screening logs	Throughout the trial							

* Intervention group only. y: years, m: months, d: days, pre-op: pre-operatively, post-op: post-operatively, q: questionnaire, AEs: adverse events

23. APPENDIX C: GUIDE FOR QUALITATIVE INTERVIEW WITH INTERVENTION PARTICIPANTS

Topic	Question	Prompt
Introduction	Thank you for taking the time for the interview. The aim of the interview is to tell me your thoughts about the diet. We welcome all comments, positive and negative and indeed sometimes the negatives comments are the most helpful, so please feel free to express your views.	
Overall view	How did you feel about finding out that the choice of having or not having the diet was done at random? Did it make sense to you why it had to be done that way? How did you feel when you find out that you were randomised to the weight loss group? How are you finding the diet?	
Delivery	How do you find your contact with the dietitian?	- Over the phone contact - Length of calls - Knowledge - Advice and support
Engagement: barriers and facilitators	What has made it difficult to attend the phone calls?	- Work - Family - Other commitments - Feeling unwell
	What has helped you to attend the phone calls?	- Improve recovery - Support by dietitian
	How do you keep track of your diet?	- Log of shakes - Log of weight - Log of blood pressure/glucose
Adherence: barriers and facilitators	How much effort do you feel you need to put in to follow the recommended diet?	
	If someone was considering starting the diet, what would you say it's like to follow the diet?	What has made it easy to stick to the diet? - Motivation to improve recovery - Support by dietitian - Weight loss - Ease of use of shakes - Being part of a trial
	If someone was considering starting the diet, what would you say they need to be aware of?	Any difficulties sticking to the diet? - Temptations - Flavour

Topic	Question	Prompt
	How has your family and friends found it while you are on the diet?	- Social occasions - Side effects - Approval/disapproval - Supportive and reinforcing / not supportive - Positive/negative comments/actions
	How have you been feeling during the diet?	- Unhappy, happy - Different compared with before starting
	How confident are you that you can continue to follow the diet? How confident are you that the diet will benefit you?	
Symptoms of both TDR and cancer	Have you had any constipation or diarrhoea? If yes, has this [constipation/diarrhoea] worried you?	
Physical activity	Have you changed your physical activity since diagnosis?	- Type - Frequency - Intensity - Length
Future research questions	We want to see how we can improve this diet in the future and we would like to ask you your honest opinion on the following. Losing more weight might improve recovery after surgery to a greater extent. However, that means delaying the surgery for a couple of weeks to lose this weight. If your surgery were to delayed by up to a couple of weeks to lose another 4 pounds/2kilos, would you have been as willing to join the trial?	
	We would like to test how this diet works together with physical activity. Now that you know how it feels to be on this diet, how would you feel if in addition to the diet, we had asked you to increase your physical activity?	If positive - type of activity e.g., walking, resistance If negative - why not, hunger, asking “too much”, too tired
	How would you feel about re-starting the diet a couple of months after you recover from surgery to help you lose more weight and improve your long-term health?	
Close down	Any further comments? Thank you for taking part in the interview.	

24. APPENDIX D: GUIDE FOR QUALITATIVE INTERVIEW WITH STAFF

Topic	Question	Prompt
Warm-up	Thank you for taking the time for the interview. Let's start by telling me your thoughts about the trial overall.	
Need for the trial	Do you feel there is clinical equipoise? What are your thoughts on the design of the trial?	Expand on yes/no answer
Attitudes	What do you think of the diet being tested? What would be your concerns about the trial and the diet? How do you think this intervention fits within the local pre-habilitation services?	
Recruitment	What are the challenges discussing this trial with patients? What, if anything, has made you not discuss the trial with a patient meeting the inclusion/exclusion criteria? How do you think patients reacted to the idea for the trial? What has made the recruitment more difficult than expected? What would make the recruitment easier?	
Trial processes	Based on your experience of the trial, what would improve the trial processes?	- Questionnaire completion - Medical records extraction - Blinding - Communication with central team
Applicability and future	How relevant the results will be to your own practice? How could it be embedded in usual care? What do you think the next steps should be?	- Diet paired with physical activity - Extension of diet pre-surgery -Extension of diet post-surgery
Co-ordination	[For research nurses and dietitians only]: How have you found the communication with the [research nurse/dietitian]? What can be done to improve this?	
Close down	Any additional comments? Thank you for taking the time for this interview.	

25. APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1.0	2.0	25 July 2023	Dimitrios Koutoukidis	Change in the exclusion criteria to allow people following vegan diets or being lactose intolerant to take part.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).