Received: 26 April 2023 | Revised: 12 June 2023 | Accepted: 19 June 2023

DOI: 10.1111/codi.16687

STUDY PROTOCOLS

CARE: Protocol of a randomised trial evaluating the feasibility of preoperative intentional weight loss to support postoperative recovery in patients with excess weight and colorectal cancer

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Funding information
National Institute for Health and Care Research

Abstract

Aim: Excess weight increases the risk of morbidity following colorectal cancer surgery. Weight loss may improve morbidity, but it is uncertain whether patients can follow an intensive weight loss intervention while waiting for surgery and there are concerns about muscle mass loss. The aim of this trial is to assess the feasibility of intentional weight loss in this setting and determine progression to a definitive trial.

Methods: CARE is a prospectively registered, multicentre, feasibility, parallel, randomised controlled trial with embedded evaluation and optimisation of the recruitment process. Participants with excess weight awaiting curative colorectal resection for cancer are randomised 1:1 to care as usual or a low-energy nutritionally-replete total diet replacement programme with weekly remote behavioural support by a dietitian. Progression criteria will be based on the recruitment, engagement, adherence, and retention rates. Data will be collected on the 30-day postoperative morbidity, the typical primary outcome of prehabilitation trials. Secondary outcomes will include, among others, length of hospital stay, health-related quality of life, and body composition. Qualitative interviews will be used to understand patients' experiences of and attitudes towards trial participation and intervention engagement and adherence.

Conclusion: CARE will evaluate the feasibility of intensive intentional weight loss as prehabilitation before colorectal cancer surgery. The results will determine the planning of a definitive trial.

KEYWORDS
colorectal cancer, diet, morbidity, prehabilitation, surgery, weight loss

Clinical trial registration: https://www.isrctn.com/ISRCTN39207707, prospectively registered.

INTRODUCTION

Colorectal cancer is the fourth most common cancer in the UK. More than 42,000 people are diagnosed annually. Surgery is the standard treatment for ~70% of patients ($n = 29{,}000$) but leads to significant postoperative morbidity. This morbidity increases the psychological and health burden of patients by a factor of 10 [1]. It also increases healthcare spending [2].

Concomitant obesity independently doubles the morbidity risk following colorectal cancer surgery (43% vs. 21% without obesity) [3]. Two thirds of patients with colorectal cancer have excess weight (of which half have obesity) at diagnosis [4]. Systematic reviews with meta-analyses show that obesity is associated with an additional day of hospital stay, a 20-min longer operation [3], serious postoperative complications (21% vs. 15%) [5], anastomotic leaks (RR: 3) [6] and double rates of conversion to open surgery compared to people without obesity, regardless of demographic characteristics [7]. In priority setting partnerships, finding effective preoperative treatments and preventing surgical complications are among the most important research questions [8, 9].

Preoperative intentional weight loss in patients carrying excess weight and awaiting colorectal cancer surgery could reduce postoperative morbidity by improving physical function, cardiovascular fitness, systemic inflammation, and glucose regulation [10–15]. The amount of weight loss needed to improve morbidity outcomes in other conditions follows a dose–response pattern. Bariatric surgery studies show that 5%–9% and ≥10% preoperative weight loss is independently associated with 31% and 42% lower 30-day mortality, respectively [16].

In the context of treating colorectal cancer, weight loss needs to be achieved within the typical 4-week window between decision to treat and surgery. A scalable way to achieve this is through a nutritionally-replete, low-energy total diet replacement programme with behavioural support (TDR). TDR reliably leads to a mean 7% (standard deviation: 1.8 kg) weight loss within 4 weeks in diverse populations with obesity-related diseases, including in older adults with obesity, and implemented in pragmatic settings [17–22].

Intentional weight loss is strongly linked with intervention adherence [23]. However, the period around cancer diagnosis is associated with feelings of uncertainty and anxiety [24, 25]. 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 [26, 27]. Patients report their cancer diagnosis being a stimulus for healthier dietary change [28, 29], but also report making only marginal changes on their own [30]. This highlights the need for support. Small mostly single-centre trials have shown feasibility in terms of recruitment (51%–53%), engagement (95%–97%), and retention (85%–97%) to less intensive preoperative dietary weight loss interventions in breast, prostate, and gastric cancers. These programmes advised an energy-restricted healthy diet or provided partial meal replacements [31–34]. Whilst these approaches support the feasibility of intervening, they achieved only small weight loss (average: 3 kg) with high variability (SD: 4–5 kg) that may be insufficient to improve surgical outcomes.

What does this paper add to the literature?

It is unknown if intentional weight loss is beneficial before colorectal cancer surgery. This paper describes the protocol of the first trial of intensive weight loss as prehabilitation treatment for patients with excess weight awaiting colorectal cancer surgery.

Contrary to this evidence of intentional weight loss in structured programmes, evidence from cohorts suggests that preoperative weight loss is associated with worse postoperative and long-term outcomes. However, it is unclear if this is attributable to unintentional weight loss and explained by selection bias due to advanced stage disease [35].

There are also theoretical concerns about muscle mass loss. However, the amount of body fat is positively associated with the amount of muscle mass [36, 37]. During intentional weight loss, muscle mass reductions are small (~3%) [38, 39], probably not clinically meaningful [40, 41], and, in older adults, weight loss significantly improves physical and cardio-metabolic fitness [10, 42]. Another trial of a very-low-energy diet in older adults showed improvements in physical function without adverse outcomes despite small reductions in lean mass [21]. Unlike some weight loss programmes, TDR, being micronutrient-rich, has been shown to improve nutritional status [21, 43], which may further contribute to beneficial outcomes [44, 45].

Accordingly, preoperative TDR may improve outcomes in this population but this hypothesis needs formal testing. A feasibility trial is required before a trial testing the intervention's effectiveness and cost-effectiveness can be conducted. For the potential of the feasibility trial to be realised, recruitment to target is key. Complex logistics and significant participant burden have been recruitment challenges in a previous randomised controlled trial of prehabilitation intervention which recruited 0.75 participants per centre per month and 51% of eligible patients [46]. Although these will be reduced by delivering and testing the CARE intervention remotely, some may remain. For example, some staff may have preconceptions about this intervention, such as a mistrust of rapid weight loss diets or lack of confidence in weight loss as a treatment [47, 48]. This may influence whether and how the trial is presented to patients. The way patients respond is also hard to predict. Their decision may be complicated by an awareness that weight loss is a symptom of advanced cancer and not perceived as an established treatment, or patients may perceive the control arm as "no treatment" and refuse randomisation. The recruitment process will require coordination and communication between doctors, research and clinical nurses, dietitians, and patients. To mitigate potential challenges, we will embed the established QuinteT recruitment process [49]. This iterative and cumulative data

collection and analysis process will allow us to understand the recruitment as it happens and iteratively develop and test ways to address identified challenges during the trial [50].

The aim of this randomised controlled trial is to assess the feasibility of intentional weight loss in this setting and determine progression to a definitive trial. The specific objectives are to assess recruitment, engagement, adherence, retention, and intervention safety.

METHODS

Study setting

CARE is a multicentre feasibility parallel randomised controlled trial with embedded evaluation and optimisation of the recruitment process. It compares a low-energy total diet replacement programme with behavioural support against standard care. It aims to recruit 72 participants from academic and community hospitals across England taking into consideration the diversity of the population in terms of geographical location and deprivation. We have particularly included sites from areas that have among the highest age-standardised colorectal cancer incidence and mortality. A list of participating hospitals is available on the study's website (https://tinyurl.com/thecarestudy).

Eligibility criteria

The study aims to recruit participants listed for curative colorectal resection for cancer with a BMI ≥28 kg/m^2 (≥25 kg/m^{2}for Black, Asian, or minority ethnic groups) [51]. Table 1 presents the key inclusion and exclusion criteria.

TABLE 1 Key inclusion and exclusion criteria.

Key inclusion criteria	Key exclusion criteria
Listed for curative elective colorectal resection for cancer	<20 days from the screening visit until surgery
BMI ≥28 kg/m^2 (≥25 kg/m^{2}for Black, Asian, or minority ethnic groups)	≥10% self-reported weight loss in the 6 months before the screening visit
Age ≥ 18 years	Documented stage 4–5 kidney disease
If neoadjuvant treatment is indicated, it must have been completed	Documented severe heart failure
Performance status 0–2	Previous bariatric surgery
	Type 1 diabetes
	Currently on warfarin
	Follows an exclusively vegan diet, having lactose intolerance, or having allergy to soy

Intervention: Low-energy total diet replacement with behavioural support

In addition to their local standard care pathway, participants will be asked to replace all their foods with a nutritionally complete package of four formula products per day (Habitual Health, Ltd). Together, these products contain approximately 800 kcal/day including 76 g protein/day with the nutritional composition subject to regulatory guidelines [52]. They will also be advised to drink >2.5 L/day of energy-free fluids and take a fibre supplement to proactively reduce the risk of constipation.

Participants will have a 45-min introductory phone consultation with a dietitian, weekly 20-min follow-up calls, and a 10-min exit call. Participants will be offered the option of having the support over video (Microsoft Teams) if they prefer. The support aims to maintain motivation during the adjustment to formula foods and problem-solve issues that arise. The support aims to build and maintain motivation, provide practical advice and feedback on changes, problem solve any barriers, and guide participants on managing social situations, coping with hunger, and avoiding and managing lapses. Participants will self-report their adherence to the intervention over the previous week on a scale 0–10 at the beginning of each dietetic consultation.

The intervention will start the day after randomisation and finish approximately 2 days presurgery (depending on local guidance for standard preoperative preparation) or when 15% weight loss has been achieved (if unexpected lengthy delays to schedule the surgery occur), whichever is earlier.

Medications for the management of type 2 diabetes and/or hypertension will be reviewed at the start of the intervention and may be adjusted to minimise the risks of hypoglycaemia, ketoacidosis, and hypotension. Specific subgroups will be asked to self-monitor their blood glucose or blood pressure throughout the intervention.

Our patient and public involvement (PPI) group felt positive about the proposed intervention as prehabilitation treatment and we incorporated their suggestions in the intervention delivery. These included offering participants the choice of their preferred flavours to enhance adherence, providing the programme from one dietitian to each participant (where possible) to ensure continuity of care, and allowing participants to choose between phone calls and video consultations.

Criteria for discontinuing the intervention include participant declining surgery, pregnancy or other ineligibility, significant protocol deviation, significant nonadherence with the intervention or trial requirements, and clinical decision.

Care as usual group

Participants will follow the local standard care pathway that may include advice and support on prehabilitation. Our PPI group felt that offering standard care, especially during uncertain times, is reassuring for patients. We will report on the standard care pathway of each recruiting hospital.

Outcomes

The primary objective of the trial is to assess whether progression to a definitive trial is justified. This is assessed based on progression criteria detailed in Table 2: the rates of recruitment, engagement, adherence, and retention as well as the safety profile.

The rate of recruitment was chosen based on the recruitment rate of another trial of prehabilitation in colorectal cancer and the average number of colorectal cancer resections per hospital [46]. The rate of retention was chosen based on the retention rate in that trial [46].The rates of engagement and adherence were based on a trial of this type of intervention in the general population [17, 23]. In all the above, the decision for cutoffs included what was deemed as reasonable to allow progression to the definitive trial.

Secondary outcomes, as detailed in the data collection methods section, include

- Morbidity based on the Clavien-Dindo classification at discharge and 30-days postoperatively (which is planned to be the primary outcome of the future definitive trial)
- Oncological outcomes (survival, resection margins, recurrence, new primary/secondary cancer)
- Operative outcomes (intraoperative blood loss, operating time, conversion to open surgery, surgical site infection, stoma rates and complications, radiologically-defined anastomotic leaks, time in intensive care unit and high dependency unit, reoperation rates, and readmission rates)
- Length of hospital stay and days alive and out of hospital
- Weight and fat-free mass
- Physical fitness based on the time for the sit-to-stand test
- Health-related quality of life, anxiety, and depression
- Costs and healthcare resource use
- Adverse events.

Process outcomes include

- Experience of the intervention and the trial based on feedback from survey questions and qualitative interviews
- Contamination of the care as usual group
- Fidelity of delivery
- Barriers to trial enrolment based on the reasons for declining participation.

Participant timeline

Table 3 presents the schedule of study procedures.

Sample size

With 72 patients ($n=36$ per arm), the trial is 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 [53]. 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 [53].

Recruitment

Recruitment opened on the 28 March 2023 and is expected to close in June 2024. Participants are recruited from at least nine NHS Trusts across England and we aim to select sites to cover multiple geographical areas. The recruitment pathway will be flexible within and across

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[1]	≥60%	36%–59%		≤35%
Retention	4	% at final follow-up	≥85%	66%–84%		≤65%
Safety	5	Safety profile	Based on related adverse events and on related expected and related unexpected serious adverse events. Adjudicated by the Trial Steering, Data Monitoring, and Ethics Committee			

[1]Non-adherence will be defined as <2% weight loss from baseline to the day of surgery.

TABLE 3 Schedule of study procedures.

	Assessments								
	From suspicion of cancer to diagnosis	From diagnosis to 3 days post diagnosis	0–4 days post randomisation	Halfway from starting intervention to surgery (±3 days)	4 days preop to day of surgery	Admission	Discharge (~5–7 days post-op)	30 days postop (27–37 days)	3 years (±6 month) postop
Procedures	Prescreening	Screening/ baseline	Preop 1	Preop 2	Preop 3	Preop 4	Discharge	Postop	Long-term follow-up
Informed consent		X							
Eligibility assessment	X	X							
Demographic q		X							
Concomitant medication		X							
Randomisation		X							
QuinteT qualitative interview			X - optional						
EQ-5D-5L q		X			X			X	
EORTC-QLQ-CR29 q								X	
HADS q		X			X			X	
Resource use q		X						X	
Preop qualitative interview[a]				X					
Feedback q presurgery[a]					X				
Feedback q post-surgery								X	
Height		X							
Weight and fat-free mass		X				X		X	
Five 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								

Abbreviations: AEs, adverse events; preop, preoperatively; postop, postoperatively; q, questionnaire.

[a]Intervention group only.

recruitment sites to allow for differences in cancer diagnostic and treatment pathways across patients and hospitals. 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 they have been (provisionally) listed for surgery. Written, video, and verbal versions of the participant information will be presented to the participants which have been codesigned with our PPI group. Participants must personally sign and date the latest approved version of the informed consent form (Appendix S1). Participants who decline to participate will be asked to provide the reasons for declining to take part by choosing all possible reasons from a pre-defined list.

Allocation

Participants will be enrolled to the study and assigned to the interventions by a researcher at their local research site. They will be individually randomised through an existing web-based central function (REDCap-Minimization version 1.2.2) on REDCap with a 1:1 allocation ratio through minimisation with a 20% random element [54]. The two stratified variables are performance status (0 vs. 1–2) and median age at diagnosis (</≥70 years). 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 at the point of randomisation.

Blinding

Due to the nature of the intervention, only the assessors of the post-operative complications at follow-up will be blinded to group allocation by not accessing relevant information that can lead to unblinding. Therefore, procedures for unblinding are not applicable.

Data collection methods

Data will be recorded by trained assessors. Weight and percentage fat will be measured barefoot and in light clothing with bioelectrical impedance (Tanita SC-240, Tanita, Netherlands). Physical fitness will be estimated with the responsive to change 5-times sit-to-stand test [55]. For health-related quality of life, anxiety, and depression, participants will fill in the following validated questionnaires with acceptable responsiveness to change: the EuroQoL-5D 5-level version (EQ-5D-5L) and the Hospital Anxiety and Depression Scale [56–59]. At the 30-day follow-up, they will also fill in the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Colorectal cancer module (EORTC-QLQ-CR29) [60]. They will also fill in a modified Client Service Receipt Inventory [61] about time off work and use of health care and social care services. Participants in the intervention group will fill in a feedback questionnaire using adapted questions from the theoretical framework of acceptability questionnaire [62], participants in the care as usual group will fill in a questionnaire on weight loss attempts between diagnosis and surgery to assess potential contamination, and all participants will fill in a study-specific feedback questionnaire assessing satisfaction with the trial processes. Fidelity of intervention delivery of the will be assessed through observation of a subsample of the consultations. Postoperative complications will be based on medical records and participant self-report. They will be graded (I–V) independently by two researchers blinded to treatment allocation with the Clavien-Dindo classification of postoperative complications, the most widely used and validated measure [63]. Operative and oncological outcomes will be extracted from medical records, including all of the proposed core outcomes [64]. Data up to 3 years postoperatively will be accessed through medical records. To promote data completeness, we will continue to be able to access medical records unless withdrawn participants explicitly tell us otherwise and participants who want to stop the intervention will be given the option to continue with the study assessments. Our PPI group considered the patient burden as acceptable.

QuinteT evaluation and optimisation of the recruitment process

QuinteT step 1: Understand recruitment as it happens

We will collect information from different sources to understand recruitment challenges (e.g., study information provision, recruitment techniques, and patient concerns) to inform how to optimise recruitment processes. First, we will conduct semi-structured phone interviews with participants and local study staff with the aim to ascertain their views on and experiences of trial delivery. Second, we will observe recruitment interactions between potential participants and the local study staff before participants decide to enrol to the trial by audio-recording with verbal permission from staff and potential participants. This strategy will reduce potential social desirability and recall bias. If potential participants decline to take part in the trial but are happy for the audio-recording to be kept and analysed, they will provide informed consent only for this aspect using a separate consent form. Finally, anonymised screening logs will be assessed using the SEAR (screening, eligibility, approach, and randomisation) framework for identification of screen failures and dropouts [65]. The combined analysis of the above will culminate in developing a "script", aiming to change problematic terms, so that equipoise is maintained in communication with patients, common concerns addressed and overall informed consent is improved.

QuinteT step 2: Feedback and script piloting

We will purposively select sites with lower initial recruitment rates to allow for rapid improvements. This analysis will explore how well recruiters follow the script, communication challenges, and clear words

and phrases to explain equipoise without inadvertently showing preferences. We will continue to monitor recruitment rates to identify whether the script improves recruitment rates in a pre-post analysis. Based on the above findings, the script will be revised and recirculated with feedback.

QuinteT step 3: Optimising recruitment

We will continue analysing audio-recordings of the recruitment interactions to fully optimise recruitment and develop a recruitment strategy for the definitive trial.

QuinteT step 4: Facilitating enrolment

We will also use information from the staff (researchers and dietitians) interviews and logs recording the time period between randomisation and intervention commencement to explore individual and structural factors influencing rapid implementation of the baseline visit, randomisation, and, crucially, intervention commencement.

Data management

Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Oxford [66, 67]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for data integration and interoperability with external sources. REDCap entries will be the source data where possible (e.g., questionnaires). Entries are embedded, as appropriate, with mandatory fields and range checks to minimise missing data and data queries. 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.

Statistical methods

We have prospectively published the statistical analysis plan for the primary outcomes (progression criteria) in the ISRCTN registry. 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 and two-sided 90% confidence intervals (given the one-sided 5% level in the sample size calculation). This uncertainty will be descriptive and will not be considered in the decision to progress to the definitive trial. All other outcomes will be summarised descriptively by trial arm and the statistical analysis plan will be made public before database lock. 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.

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 nonadherence. A per protocol analysis will include the subsample of intervention participants who achieved ≥5% weight loss from baseline to the day of surgery, because weight change is a valid surrogate for intervention adherence and bariatric surgery literature suggests this to be a minimally clinically significant difference [16]. Missing data are applicable only for the progression criterion of adherence. For adherence (i.e., weight loss), missing data will be imputed using methodology deemed appropriate by the trial statistician given the magnitude of the missing data and any other factors deemed relevant at the time. This imputation is likely to be through baseline observation carried forward, because (a) the duration between the two time points is short (~4 weeks) during which weight typically remains relatively stable, (b) we anticipate a relatively small proportion of missing data as the follow-up visit happens on admission to hospital, and (c) the total size of the study is small.

Monitoring

As this is an unblinded trial (with blinded outcome assessment), a separate data monitoring and ethics committee is not required. The trial steering committee will also assume the role of the Data Monitoring and Ethics Committee. It comprises a Chair, two academics, a statistician, and a patient and public representative, all of whom being independent of the sponsor with no competing interests.

No interim analysis is planned and, therefore, the progression criteria (Table 2) will be analysed at the end of the study. The trial steering committee may formally recommend early termination if needed in line with its charter, which is available upon reasonable request.

Patients will self-report potential adverse events. These will be recorded on REDCap using standardised forms and reported to the sponsor and the ethics committee in line with standard guidance. In previous studies of this intervention, one in five people experience an adverse, mostly mild, event due to the intervention [17]. Constipation (1 in 7), fatigue (1 in 12), headache (1 in 17), and dizziness (1 in 22) are the most common adverse events albeit mild (only 11% were moderate or severe) less severe over time, and temporary [17, 18]. The dietitian will support the participants in managing potential adverse events. Operative and postoperative complications that could meet the definition of serious adverse events will not be reported as such, as they will be reported as part of the study outcomes, but the trial steering committee will monitor the frequency of complications and may advise reporting at their discretion.

Auditing

The Surgical Intervention Trials Unit will regularly monitor trial performance against established standard operating procedures. At their discretion, the sponsor and trials unit may audit the trial conduct. The process will be independent from investigators.

Protocol amendments

Protocol amendments will be implemented only following notification and/or approval by the REC, as appropriate. They will be communicated to the trial registry and outlined in publications.

Archiving

Following review to ensure participant anonymity is safeguarded and subject to any reasonable and necessary delay, anonymised research data will be securely archived to a repository following publication of the results where they will be stored indefinitely. De-identified data will be available on reasonable request to researchers with a specific analysis plan.

Data access

Throughout the study, the trial steering committee, trials unit, data manager, and statistician will have access to the whole dataset but the central investigators will not have detailed access to the adverse events and complications, as these are core outcomes of the definitive trial. Following database lock, central investigators will get access to the full trial dataset. Local principal investigators will have direct access only to their own site's datasets and may have direct access to the full dataset on reasonable request to the central investigators with a specific analysis plan.

Ancillary and post-trial care

The sponsor 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. NHS indemnity operates in respect of the clinical treatment that is provided.

Dissemination policy

The investigators will review drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Publication of results will not depend on the direction of findings. Participants will receive a lay summary of the findings. Results will be disseminated to the research sites and more widely through relevant charities and professional groups. Authorship will be determined in accordance with the ICMJE guidelines. The full protocol will be appended to the primary publication.

DISCUSSION

Despite multiple prehabilitation interventions, there is a lack of robust evidence of their effectiveness and cost-effectiveness in improving recovery. This leads to guidelines only weakly recommending prehabilitation interventions [68, 69]. This feasibility trial will assess whether an intensive weight loss programme is feasible in patients awaiting colorectal cancer surgery. If the progression criteria are met, we aim to apply for funding to conduct a definitive trial on whether this intervention is effective in reducing postoperative complications after colorectal cancer surgery in a cost-effective manner among patients with excess weight.

Although most prehabilitation trials have tested physical activity interventions, we opted not to include a physical activity component in our trial due to their limited evidence of effectiveness so far [70], the need for a factorial trial to disentangle diet and activity effects, and avoiding asking "too much" of participants while they are trying to adapt to an intensive dietary regime. However, we recognise the importance of physical activity for overall health and participants in both groups will receive guidance in line with the UK physical activity recommendations and standard care.

Our study design promotes enrolment of generally underrepresented groups by providing the intervention for free to participants, catering for dietary requirements, recruiting from diverse areas across the country, having ethnic-specific definitions of overweight, and enabling patients who do not speak English to take part. We anticipate that the embedded processes for evaluation and recruitment optimisation will inform the future trial and facilitate recruitment. This will be crucial, because a previous efficacy trial of prehabilitation before colorectal cancer surgery had a planned sample size of 1,146 patients to detect a minimally clinically meaningful 25% relative reduction in morbidity [71]. Furthermore, feasibility and safety data from the trial may help counteract barriers such as lack of culture to use dietary interventions beyond simple advice, lack of time, fear of causing offence, doubts about effectiveness, and perceptions that "weight gain is good and weight loss is bad" [48]. Alternatively, data may caution against intentional weight loss in this group.

Adoption of effective interventions into practice depends critically on cost-effectiveness. The relatively low cost of a 4-week TDR programme [72, 73] compared with the average cost of postoperative morbidity in colorectal cancer might make this intervention cost-effective. We will estimate potential costs and benefits during the study to guide the future definitive trial.

AUTHOR CONTRIBUTIONS

Dimitrios Koutoukidis A: Writing – original draft; methodology; investigation; funding acquisition; conceptualization. **Susan Jebb A:** Conceptualization; investigation; funding acquisition; methodology.

Claire Foster: Conceptualization; investigation; funding acquisition; methodology. **Pete Wheatstone:** Investigation; funding acquisition; methodology. **Alison Horne:** Methodology; validation; software; data curation. **Martyn Hill T:** Methodology. **Amy Taylor:** Resources; project administration; validation. **Alba Realpe:** Investigation; methodology. **Felix Achana:** Investigation; funding acquisition; methodology.

FUNDING INFORMATION

This project is sponsored by the University of Oxford and funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (grant reference no. NIHR204051). DAK is also supported by an NIHR Advanced Fellowship (NIHR302549). SAJ is also funded by the Oxford NIHR Applied Research Collaboration. SJAB is supported by The Pharsalia Trust, UK and Cancer Research UK Advanced Clinician Scientist Fellowship (C14094/A27178). The funder has no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The sponsor has no role in the collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The ultimate authority over any of these activities lies with the study investigators. The views expressed are those of the author (s) and not necessarily those of the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This research has received ethical approval by the South Central - Oxford B Research Ethics Committee (Ref: 22/SC/0465).

PATIENT CONSENT STATEMENT

All participants will provide written informed consent.

INDEPENDENT TRIAL STEERING, DATA MONITORING, AND ETHICS COMMITTEE

Mr James Hernon (chair), Dr Michelle Harvie, Dr Richard Parker, Mr Andrew Bates and Ms Lindy Berkman.

TRIAL MANAGEMENT COMMITTEE

All named investigators, the trial manager, relevant staff from the Surgical Intervention Trials Unit, and other key personnel involved in the trial.

PROTOCOL VERSION

v3.0, 27 February 2023.

SPONSOR'S CONTACT INFORMATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Koutoukidis DA, Jebb SA, Foster C, Wheatstone P, Horne A, Hill TM, et al. CARE: Protocol of a randomised trial evaluating the feasibility of preoperative intentional weight loss to support postoperative recovery in patients with excess weight and colorectal cancer. Colorectal Dis. 2023;25:1910–1920. https://doi.org/10.1111/codi.16687