CARE

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

(Short title: Could supported weight loss reduce bowel cancer surgery complications?)

Statistical Analysis Plan

Version v1.0 14Mar2023

Linked to SAP - Data Definitions and Tables
Version to be determined

Based on Protocol version v3.0 270223

Trial registration: IRAS Project ID: 320173

Surgical Intervention Trials Unit (SITU)

SURGICAL INTERVENTION TRIALS UNIT

CONTENTS

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the National Institute for Health Research-funded study named "Pre-operative intentional weight loss to support post-operative recovery in patients with overweight and colorectal cancer: the CARE feasibility randomised controlled trial". The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. This document follows published guidelines regarding the content of statistical analysis plans for clinical trial (Gamble et al).

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy. If reported, the analyses will be marked as post-hoc and the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician or researcher, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

Integral to this Statistical Analysis Plan (SAP) is the SAP – Data Definitions and Tables document which will include full detailed descriptions of all key outcomes, including their definition, generation and how they will be reported at the end of the study. These two documents should be read in tandem.

1.1 Key personnel

Author(s)

- Martyn Hill (Trial Statistician since inception): martyn.hill@nds.ox.ac.uk

Reviewers

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- Others as required

Approver (Chief Investigator and others)

- Chief Investigator: Dr Dimitrios Koutoukidis
- Others as required, including Martyn Hill (Trial statistician).

1.2 Changes from previous version of SAP

This is a summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. The protocol version number and date are included.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V0.1_08Dec2022	Martyn Hill	CARE protocol v1.0 181122	Not applicable as this is the 1st issue
v0.02_06Feb2023	Dimitrios Koutoukidis	CARE protocol v1.0 181122	First draft
v0.03_21Feb2023	MH & DK	CARE protocol v1.0 181122	Second draft
V1.0_14Mar2023	MH & DK	CARE protocol v3.0 270223	Clean version 1.0
			Add to or delete as required

2. BACKGROUND AND OBJECTIVES

2.1 Brief synopsis

This trial is a study of a pre-operative intentional weight loss intervention intended to support post-operative recovery in patients with overweight and colorectal cancer, aka "the CARE feasibility parallel randomised controlled trial". It is intended to examine the feasibility of progression to a definitive randomised controlled trial that will examine whether a supported weight loss intervention aimed at overweight adults awaiting colorectal cancer surgery can reduce complications.

3. STUDY METHODS

3.1 Trial Design/framework

See also the protocol section "Study Design", "Synopsis", "Description of the Statistical Methods"

This is a prospective randomised controlled trial (RCT) with two arms, one for the intervention, one for the control. The timing is as follows

- Total trial length: 5.5 years
- Recruitment period: approx. 16 months (planned for March 2023 to June 2024)
- Individual participant's involvement: approx. 2-3 months
- Long-term follow-up via medical records: up to 3 years

The trial will have an embedded evaluation and optimisation of the recruitment process (QuinteT). 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 surgery), and 30 days post-operatively. They will also remotely complete questionnaires at 1-3 days pre-operatively and have a semi-structured qualitative interview over the phone. The intervention will be delivered over the pre-operative period.

The study flow-chart can be seen in the appendices. At the end of follow-up the outcomes will be summarised and presented.

3.2 Randomisation and Blinding

See also the protocol section "Randomisation" and "Blinding and code-breaking"

Participants will be randomised by the local research team intended to conduct randomisation through a minimisation module on REDCap.

There are two arms, one for the intervention, one for the control.

Eligible participants will be individually randomised with a 1:1 allocation ratio to receive either the intervention or the control through minimisation with a 20% random element. The two stratified variables will be performance status ("0" vs "1-2") and age at diagnosis ("< 70 years" and "≥70 years") with the threshold of 70 chosen as the median age of diagnosis of colorectal cancer.

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.

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. The central study team (chief investigator and members of the trial management committee) will be blinded to the adverse events and all post-operative data by trial group. The trial statistician is not blinded.

Full details of the randomisation are available in the latest RBP (Randomisation and Blinding Plan), which is stored in the confidential statistical section of the TMF.

3.3 Sample Size, hypothesis testing, and progression decision

See also the protocol section "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 the table 1 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. The collective power for the three criteria of engagement, adherence, and retention is 85% (93%*92%*99%)[4] at 5% level to detect "GO" signals, without multiple testing adjustment. Recalculating the sample size on a binomial approach (sensitivity analysis) provided almost identical estimates.[1]

We are testing against the upper limit of the red zone when the lower limit of the green zone is hypothesised to be true, therefore:

- Null hypothesis: True feasibility outcome is not greater than the upper limit of the red zone.
- Alternative hypothesis: True feasibility outcome is greater than the upper limit of the red zone.

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

See also the protocol sections "Decision Points", "Stopping Rules" and "Study Committees"

3.4.1 Interim Analysis

No interim analysis is planned.

3.4.2 Stopping rules

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

3.4.3 Trial Steering, Data Monitoring, and Ethics Committee (TSDMEC)

As this is an unblinded trial (with blinded outcome assessment), a separate Data Monitoring and Ethics Committee (DMEC) is not required. The independent Trial Steering Committee (TSC) will instead assume the role of the Data Monitoring and Ethics Committee. The resultant TSDMEC will comprise of an independent Chair (academic colorectal surgeon), two independent academics, independent statistician, and a patient and public representative.

3.5 Timing of Final Analysis

See also the protocol section "Decision Points"

The final analysis will occur at the end of the trial and no interim analysis is planned.

3.6 Blinded analysis

See also the protocol section "Blinding And Code-Breaking"

The nature of the study precludes the majority of blinding, however the central study team (chief investigator and members of the trial management committee) will be blinded to the adverse events and all post-operative data by trial group. The study statistician, who will not be blinded to these data, will prepare relevant reports of these data that will be reviewed in the closed sessions of the Trial Steering, Data Monitoring, and Ethics Committee.

3.7 Statistical Analysis Outline

The statistical analysis of the study's three primary outcomes and other outcomes is detailed in the protocol section "Statistics And Analysis", a summary of which is given below:

The study is a feasibility study intended to derive data, not to conduct formal statistical tests on them. Consequently, the outcomes will be summarised and described, not subjected to tests.

Table(s) 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. Any specific statistical analysis of the data will be carried out using appropriate statistical software. Any other analysis done by the Trial Statistician will be done by that software deemed sufficient by the Trial Statistician.

The data fall into two broad categories: the *primary outcomes* (referred to as "trial progression criteria") and the *secondary and other outcomes*. They are treated as follows:

3.7.1 Primary outcomes (referred to as "trial progression criteria")

The trial progression criteria 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 as well with 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.

Table 1: Primary variables (referred to as "trial 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

Sufficient levels of		Criterion Decision	Green Progress	Amber Progress with changes		Red Stop
	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 and related expected and related unexpected serious adverse events. 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.

In accordance with the multi-criteria aim, the decision to proceed would take into account

- Signal on criterion 1 (recruitment)
- Signal on criterion 5 (safety)

And if 1 and 5 are satisfactory (i.e., at least "amber"), the decision to progress will be based on the worst signal:

➢ If signal = RED for criteria 2 or 3 or 4 -> overall signal is RED

➢ Else, if no signal is RED but signal = AMBER for criteria 2 or 3 or 4 -> overall signal is AMBER

➢ Else, if signal = GREEN for criteria 2 and 3 and 4 -> overall signal is GREEN

3.7.2 Secondary and other outcomes

All other outcomes will be summarised descriptively by trial group. 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. Further details regarding the secondary outcomes will be provided at a later date, (provisionally in a supplementary document) prior to database lock. Both absolute and relative effect sizes will be reported.

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.

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

See also the protocol section "The Level of Statistical Significance"

P-values will not be reported given the feasibility nature of the trial.[2] There will be no adjustment for multiple testing.[3] The 95% confidence intervals will be presented but regarded as nominal and descriptive.

4.2 Definition of Analysis Populations

See also the protocol section "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.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

This is a summary of flow of trial participants through the trial and baseline stratification, demographic and clinical characteristics of each group.

5.1 Representativeness of Study Sample and Patient Throughput

See also the protocol appendix "Study Flow Chart" and the appendices in this SAP.

The flow of participants through each stage of the trial, including numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome is provided following the appropriate guideline (e.g. CONSORT flow diagram). Protocol violations/deviations and information relating to the screening data including the number of ineligible patients randomised, together with reasons, information on number of participants screened, found to be ineligible (with reasons where available), refused to participate (with reasons where available) will be included as applicable.

The trial flowchart is given in the Appendices.

5.2 Withdrawal from treatment and/or follow-up

See also the protocol section "Informed Consent" and section "Early Discontinuation/Withdrawal of Participants"

Once enrolled and during the course of the study a participant may choose to withdraw early from the intervention at any time for any reason. 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

The numbers (and percentages) of withdrawals will be reported by treatment group along with the reasons for these withdrawals. These will be summarised as per the table below.

Table 2. Details Of Withdrawals (And Reasons) Split By Treatment Group

Treatment	Patient ID	Date of withdrawal (DDMonYYYY)	Reasons for withdrawal
Intervention	ID 1		
	ID 2		
	…		
Control	ID 1		
	ID 2		
	…		

5.3 Baseline Characteristics

See also the protocol sections "Baseline Assessments" and the relevant tables in the SAP DDT

The baseline face-to-face assessment will be conducted during the screening visit at each site. Baseline characteristics are reported by treatment group, including the stratification/minimisation factors and any other variable deemed relevant.

Numbers (with percentages) for binary and categorical variables and mean (and standard deviation), or median (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

5.4 Unblinding

See also the protocol section "Blinding and code-breaking"

The nature of the study precludes blinding of participants and research nurses. Unblinding of the central research team and independent assessors of the post-operative complications (as per 3.2 and 3.6) may occur only following recommendations of the TSDMEC.

5.5 Treatment Adherence with Details of Intervention

See also the protocol sections "Protocol Deviations", "Study Monitoring" and "Serious Breaches"

The number of people in each arm receiving their randomised treatment will be reported. The adherence of the randomised participant to the intervention and control pre-surgery will be checked and reported as per the protocol. Adherence with the protocol and the SOPs and any post-surgery complications will be checked and reported as per the protocol.

5.6 Reliability

The REDCap database will incorporate range and logic checks. Manual checks may be carried on the data to ensure plausibility on the recognisance of the Trial Statistician.

6. ANALYSIS

6.1 Outcome Definitions

See also the protocol section "Synopsis"

The primary variables for this trial are referred to as "trial progression criteria" and a list of those primary outcomes is given below. The study also has secondary outcomes (morbidity, oncological outcomes, etc) which are not listed separately here as a comprehensive list can be found in the "synopsis" section of the protocol.

Table 3: a simple list of all primary variables and their measurement

Type	Objectives	Outcome Measures	Definition
Primary (Recruitment)	1a. Recruitment variable	Recruitment Rate	n of patients recruited per site per month
Primary (Recruitment)	1b. Recruitment variable	Number of sites open	Integer (0-n)
Primary (Recruitment)	1c. Recruitment variable	Total number of participants recruited	Integer (0-n)
Primary (Safety)	5. Safety profile	Based on related adverse events and expected related and unexpected related serious adverse events	Type, number of and percentage of each event category.
Primary (Engagement)	2. Engagement variable	Proportion of phone calls answered. This is defined as the "mean percentage of phone calls answered per participant"	Percentage (0-100%)
Primary (Adherence)	3. Adherence variable	Proportion of intervention participants with ≥5% weight loss from baseline to the day of surgery	Percentage (0-100%)
Primary (Retention)	4. Retention variable	% at final follow-up	Percentage (0-100%)

6.2 Analysis Methods

See section 3.7 "Statistical Analysis Outline"

6.3 Missing Data

See also the protocol section "Procedure For Accounting For Missing, Unused, And Spurious Data"

For the analysis of each of the progression criteria, the following will apply:

1. Recruitment: missing data are not applicable, so they will not be imputed.
2. Engagement: missing data are not applicable, as instances of expected consultations with which participants do not engage will be coded as "no engagement" rather than as missing.
3. Adherence: It is plausible that weight data may be missing. 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 of (a) the short duration (~4 weeks) between the two time points (screening and admission) 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.

4. Retention: missing data are not applicable, so they will not be imputed.

6.4 Sensitivity Analysis

No sensitivity analyses are planned. Should the data during the study begin to deviate from that expected (eg a non-nominal amount of missing data) then appropriate sensitivity analyses may be undertaken at the discretion of the Trial Statistician.

6.5 Pre-specified Subgroup Analysis

See also the protocol section "Description of the Statistical Methods"

No subgroup analyses are planned.

6.6 Supplementary/Additional Analyses and Outcomes

No supplementary analyses are planned.

6.7 Harms

Safety is an outcome variable and its analysis is detailed elsewhere in this document in sections such as the section "Statistical Analysis Outline" and others.

6.8 Health Economics and Cost Effectiveness (where applicable)

See also the protocol section "Health Economic analysis"

The health economics analysis plan will be reported separately.

7. VALIDATION OF THE PRIMARY ANALYSIS

See also the protocol section "Description Of The Statistical Methods"

To validate the primary outcomes a statistician not involved in the trial will independently repeat the analyses detailed in this SAP. The results will be compared and any unresolved discrepancies will be reported in the Statistical Report (See OCTRU SOP STATS-005 Statistical Report).

Table 4: list of outcome variables subject to checks by uninvolved statistician

Type	Subtype	Outcome variable (as defined in table 3)
Primary	2. Engagement variable	Proportion of phone calls answered
Primary	3. Adherence variable	Proportion of intervention participants with ≥5% weight loss from baseline to the day of surgery
Primary	4. Retention variable	Percentage at final follow-up
Primary	1a. Recruitment variable	Recruitment Rate

Primary	1b. Recruitment variable	Number of sites open
Primary	1c. Recruitment variable	Total number of participants recruited

8. SPECIFICATION OF STATISTICAL PACKAGES

Any specific statistical analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS, or R. Any other analysis done by the Trial Statistician will be done by that software deemed appropriate by the Trial Statistician. The relevant package and version number of any software used will be recorded in the Statistical Report.

9. PUBLICATION

See also the protocol sections "Ethical And Regulatory Considerations"

This study will be conducted as part of the portfolio of trials in the Surgical Intervention Trials Unit (SITU), a Royal College of Surgeons of England specialist trials centre dedicated to evaluating surgical intervention at the University of Oxford. It will follow their Standard Operating Procedures ensuring compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and any applicable regulatory requirements.

10. REFERENCES

1. Lewis M, Bromley K, Sutton CJ, et al. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! *Pilot Feasibility Stud* 2021;7(1):40. doi: 10.1186/s40814-021-00770-x [published Online First: 2021/02/05]
2. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Pilot Feasibility Stud* 2016;2:64. doi: 10.1186/s40814-016-0105-8
3. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol* 2017;46(2):746-55. doi: 10.1093/ije/dyw320 [published Online First: 2016/12/28]
4. Lewis, M., Bromley, K., Sutton, C.J. et al. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back!. Pilot Feasibility Stud 7, 40 (2021). , see link at https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-021-00770-x, see also DOI at https://doi.org/10.1186/s40814-021-00770-x

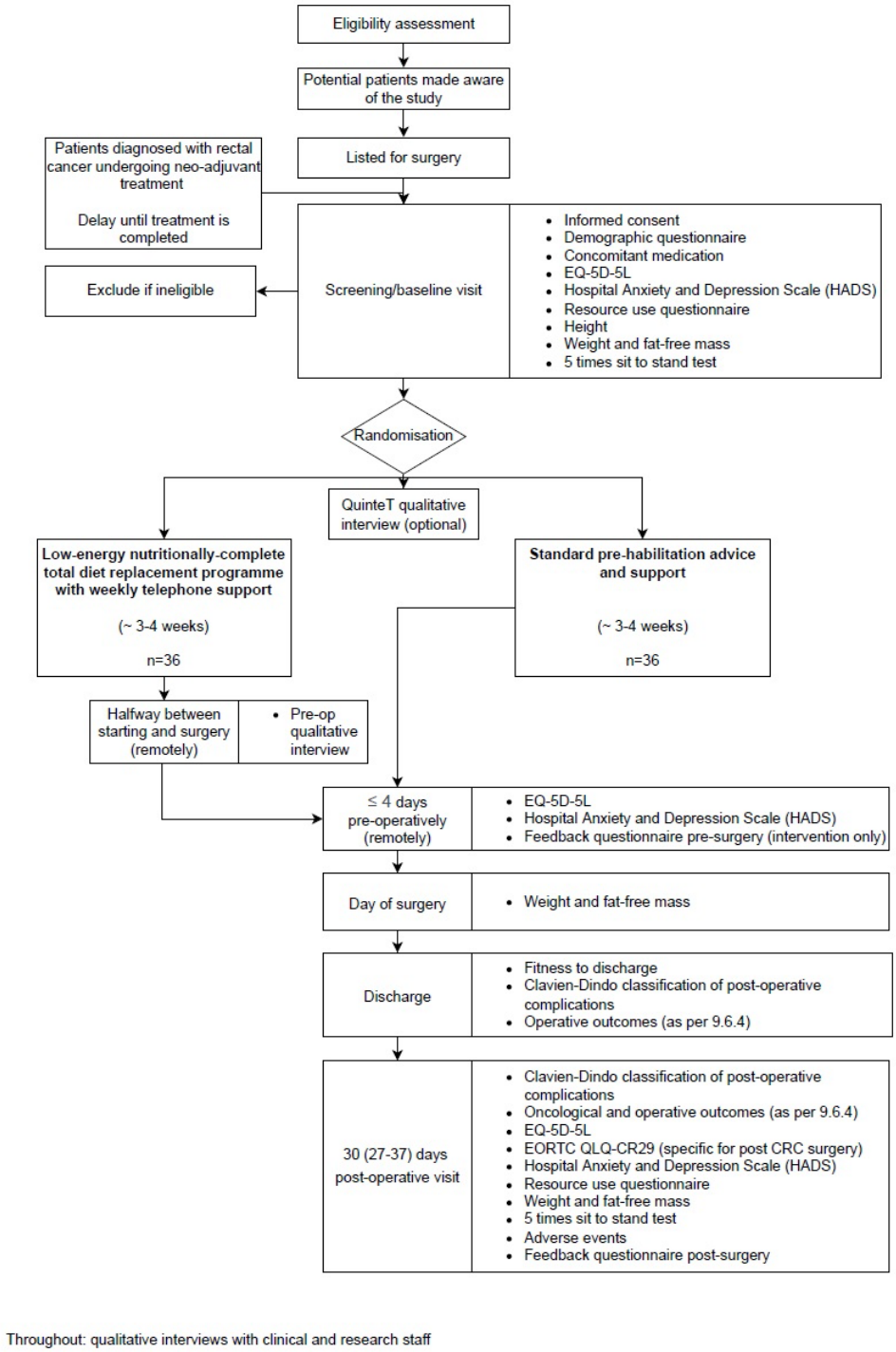
APPENDIX: GLOSSARY OF ABBREVIATIONS

Table: Glossary of abbreviations

Abbr	Meaning
CARE	CARE feasibility randomised controlled trial
DMEC	Data Monitoring and Ethics Committee (DMEC)
RBP	Randomisation and Blinding Plan
RCT	Randomised Controlled Trial
RRAMP	Registration / Randomisation and Management of Product, a randomisation software for REDCap
SAP	Statistical Action Plan
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	The independent Trial Steering Committee (TSC)
TSDMEC	Trial Steering, Data Monitoring, and Ethics Committee (TSDMC)

APPENDIX: STUDY FLOWCHART

Figure 1: Trial Flowchart



The trial flowchart is given in the Appendices. It was copied from the appendix "STUDY FLOW CHART" in the protocol and formed a standalone image called "Care Trial flowchart.jpg"