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Evaluation of a comprehensive prehabilitation intervention in frail colorectal cancer patients: A randomised pilot study protocol

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ABSTRACT

Introduction: Surgical interventions can significantly impact the functional status of patients. Prehabilitation interventions have shown efficacy in the orthopaedic and cardiothoracic surgical populations, but there has been more limited evidence for general surgical patients. We present a pilot trial of a novel prehabilitation intervention, consisting of a comprehensive preoperative assessment and treatment by a physiatrist.

Methods and Analysis: A single-centre pilot randomised controlled trial comparing comprehensive prehabilitation versus routine care for a 4- to 6-week preoperative period. 60-80 participants with colorectal cancer awaiting surgery will be block-randomised to prehabilitation versus control. Participants in the prehabilitation arm will undergo assessment by a physiatrist and enrol in a supervised exercise program. Outcome assessment at baseline and postoperatively at 1-2 weeks, 2 months and 6 months. Outcomes include fitness by 6-minute walk test (6MWT); function with the UK Functional Independence Measure and Functional Assessment Measure (UK FIM+FAM); quality of life by the Edmonton Symptom Assessment System (ESAS) and Short Form 36 questionnaire (SF-36); and postoperative complications.

Ethics and Dissemination: This study has been approved by the Hamilton Integrated Research Ethics Board (HIREB reference number 2015-0090-GRA). The results of this pilot study will be used to design a full-scale study and published in peer-reviewed journals.

Trial Registration Number: NCT02531620 (clinicaltrials.gov)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to investigate the effect of a comprehensive prehabilitation intervention on the postoperative recovery of colorectal surgery patients
- This evaluation of an intervention to address patient functional recovery in domains other than fitness addresses a gap in the current literature
- The small size of this pilot is intended to estimate effect sizes and determine feasibility for a full-scale trial
- This pilot has insufficient statistical power to detect outcome differences between groups
- This trial is limited to a colorectal surgical patient population at a single academic centre

INTRODUCTION

Surgical interventions are significant stressors, particularly to the comorbid patient, which can significantly decrease their functional ability. In order to return to independent or assisted living at home, a minimum functional level is required[1]. This includes all physical and cognitive aspects of function.

Prehabilitation for elective surgical patients may be an effective intervention to improve baseline functional reserve, which is theorized to allow the postoperative patient to more quickly reach their minimal functional level. Study of prehabilitation interventions in cardiac and thoracic surgery patients have shown decreases in pulmonary complications, measures of physical function, and length of stay[2–4]. Studies in orthopaedic patients have also shown improvement in postoperative musculoskeletal performance[5].

Most studies in the general surgical population have demonstrated that it is possible to improve preoperative fitness, postoperative fitness and respiratory function[6–9]. One study showed significant improvement in functional status by Functional Independence Measure (FIM) score, and several others show improvement in self-reported quality of life measures[7,10]. A recent meta-analysis showed a statistically significant decrease in pooled postoperative complications, but there was significant heterogeneity in the interventions studied[11]. There continues to be no evidence of an effect on hospital length of stay[10].

Nearly all trials focused on the fitness aspect of prehabilitation, which is only one aspect of global patient functional status.

Our pilot study uses a comprehensive physiatrist assessment as the main intervention. We note that the population of patients undergoing elective cancer resections are significantly different from the orthopaedic and cardiovascular patient populations. For this reason, it is hypothesized that a comprehensive assessment may do more to improve patient functional status than a fitness intervention alone. There continues to be a need for primary data in this area, and this study hopes to provide more insight into the question.

METHODS AND ANALYSIS

This study is a single-centre pilot randomised controlled trial to examine the effect of a comprehensive prehabilitation intervention versus routine care. The primary objective of this study is to determine the feasibility of conducting an adequately powered study with a similar design and intervention. The secondary objective is to assess the effect of the intervention on measures of patient outcomes, including fitness, quality of life, and perioperative complications. The study design is shown in figure 1.

The study will be conducted at St. Joseph's Healthcare Hamilton, a large Canadian urban academic hospital. Appropriate research ethics board approval has been obtained for this study.

Participants

We anticipate recruiting 60-80 study participants (30-40 per group) to the study over the course of 6-8 months. A pilot of this size is relatively large, and is primarily driven by a desire to reach a rough estimate of the effect size. For a moderate to small effect, a study size of approximately 60-80 participants would be most likely to be sufficient. Feasibility and attrition rate would also be adequately addressed with a pilot of this size[12].

Inclusion criteria:

Adults with age > 18; diagnosis of primary colorectal cancer appropriate for resection; English-speaking or with accessible interpreter; and frail, based on a score of 1 or greater on the Cardiovascular Health Study (CHS) frailty scale[13] or a history of falls in the past month, stroke or chronic pain.

Exclusion criteria:

Need for emergent resection or procedure; and extensive metastatic or unresectable disease.

Recruitment and Randomisation

Consenting patients referred to a study surgeon for colorectal cancer assessment will be evaluated by the research coordinator for eligibility. Written informed consent will be obtained from all study participants by the study coordinator prior to randomisation.

Study participants will be randomised with an equal (1:1) chance of being allocated to one of the two arms. A computer-generated randomisation log will be created by the study biostatistician. This log will be input into REDCap[14], a secure computer-based research system, and used sequentially to perform randomisation. Blocked randomisation will be used to ensure an equal number of participants in each arm. Randomisation allocation will occur by the study coordinator accessing the REDCap randomisation log at the time of enrolment.

Study Arms

Participants in the study will be randomised to either an intervention or control arm. The intervention arm will undergo a complete preoperative assessment by a physiatrist, followed by directed prehabilitation interventions to address functional or cognitive barriers to successful postoperative rehabilitation. The control group will undergo routine preoperative care. Following a 4- to 6-week preoperative period, both groups will proceed to their scheduled operative procedure.

Control Group

The control group will undergo no specific intervention in the preoperative period. This reflects the current standard of care.

Intervention Group

The intervention arm will be seen within 1 week after initial referral for a comprehensive assessment by a physiatrist. Following initial assessment, the participant will be given recommendations for preoperative optimisation. Qualifying participants will also be enrolled in the CanWell supervised exercise program[15]. There will be a 4- to 6-week period from initial consultation to operative resection in which the recommendations will be put into place.

The assessment by the study physiatrist will provide recommendations for preoperative optimisation. This may include: starting treatment for unrecognized chronic disease; recommending appropriate referrals for comorbidities; arranging appropriate home modifications based on functional status; reducing polypharmacy as appropriate; arranging early education and motor skills assessments to prepare for stoma care; and recommending follow-up or further consultations in the postoperative period.

Outcome Assessments

This pilot trial will assess feasibility of a full study by collecting estimates of recruitment rate, attrition, and effect size. Subjective feasibility data regarding study instruments and measures will also be collected.

Participant outcome measures of fitness, symptoms, function, and quality of life will be assessed at initial enrolment, and postoperatively at 1-2 weeks, 2 months and 6 months. At each follow-up, the research coordinator will assess fitness using the 6-minute walk test (6MWT)[16], and functional status using the UK Functional Independence Measure and Functional Assessment Measure (UK FIM+FAM) tool[17]. Symptoms and quality of life will be self-reported by the participant using the following validated measures: the Edmonton Symptom Assessment System (ESAS) [18], the Short Form 36 health survey (SF-36)[19], pain on a Visual Analogue Scale (VAS)[20], and the Bowel Function Index (BFI)[21].

Complications will be collected independently by both the operating surgeon and study team, and classified using the Clavien-Dindo scale[22]. In addition, mortality within 30 days, length of stay, readmissions within 6 months will also be collected by the study team.

Statistical Analysis

The analysis will follow intention-to-treat principles. Descriptive statistics will be performed. The recruitment rate and attrition rate will be reported as relative frequencies with 95% confidence intervals. Secondary outcomes data will be analysed with a *t* test, Mann-Whitney *U* test, χ^2 test or Fisher's exact test as appropriate. Other feasibility issues will be assessed subjectively.

Blinding

Due to the nature of the prehabilitation intervention, it is not possible to blind the study staff and participants. Statistical analysis of outcomes will be blinded to study arm.

ETHICS AND DISSEMINATION

The main objective of this study will be to collect pilot data to support the design of a full-scale clinical trial. Study results will also be presented in relevant scientific meetings and published in peer-reviewed journals.

This trial has been approved by the Hamilton Integrated Research Ethics Board (HIREB; reference number 2015-0090-GRA), which has the independent authority to audit trial conduct. Any amendments to the trial protocol will be submitted to HIREB for approval. The trial is registered with clinicaltrials.gov with the study identifier NCT02531620 since August 15, 2015.

Adverse Events

The main adverse events anticipated in this study are risks of injury or harm occurring during the exercise intervention. To minimize the risk of harm, participants are evaluated by their surgical team, the study physiatrist, and the study coordinator for contraindications to exercise during the initial assessment. During the exercise intervention, the participant is continuously monitored by physiotherapy staff. Any patient with contraindications to exercise will be excluded from the exercise program, but will continue with the other prehabilitation interventions.

Data Management and Monitoring

Study data will be stored on a secure, encrypted electronic system using the REDCap research system. Any data that must be retained in paper format will be stored in a secure location, accessible only to the study team. Due to the small sample size, no data monitoring committee will be established and no interim analyses will be performed.

Participant Considerations

Participants will not be remunerated for their participation in this study. All fees associated with the study will be reimbursed, including parking fees for study appointments and membership fees for the supervised exercise program.

Participants may withdraw their consent for participating in this study at any time, and will be given an opportunity to give reasons for withdrawing from the study. Participants who withdraw from the study will continue to receive routine surgical care.

DISCUSSION

The primary goal of this study is to collect feasibility data in support of a full-scale study in the future. In addition, data will be collected to improve and focus the prehabilitation intervention for the full-scale study. To our knowledge, this is the first trial to study the feasibility of a comprehensive prehabilitation intervention for colorectal cancer patients.

AUTHORS' CONTRIBUTIONS

NA conceived the idea of the study. SGW led protocol development, wrote early drafts of the study protocol, prepared the Institutional Research Board submission, and is responsible for the day-to-day conduct of the study. EM and DH provided rehabilitation and physical medicine expertise, and performed clinical functional status assessments. All authors commented on this protocol.

STUDY FUNDING

This study is funded by a grant from McMaster Surgical Associates at McMaster University. The funding body has no involvement with the design, execution or authorship of this study.

COMPETING INTERESTS

Drs. Wong, Maida, Harvey and Amin have no conflicts of interest or financial ties to disclose.

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FIGURES

Figure 1: Study Participant Flow Chart

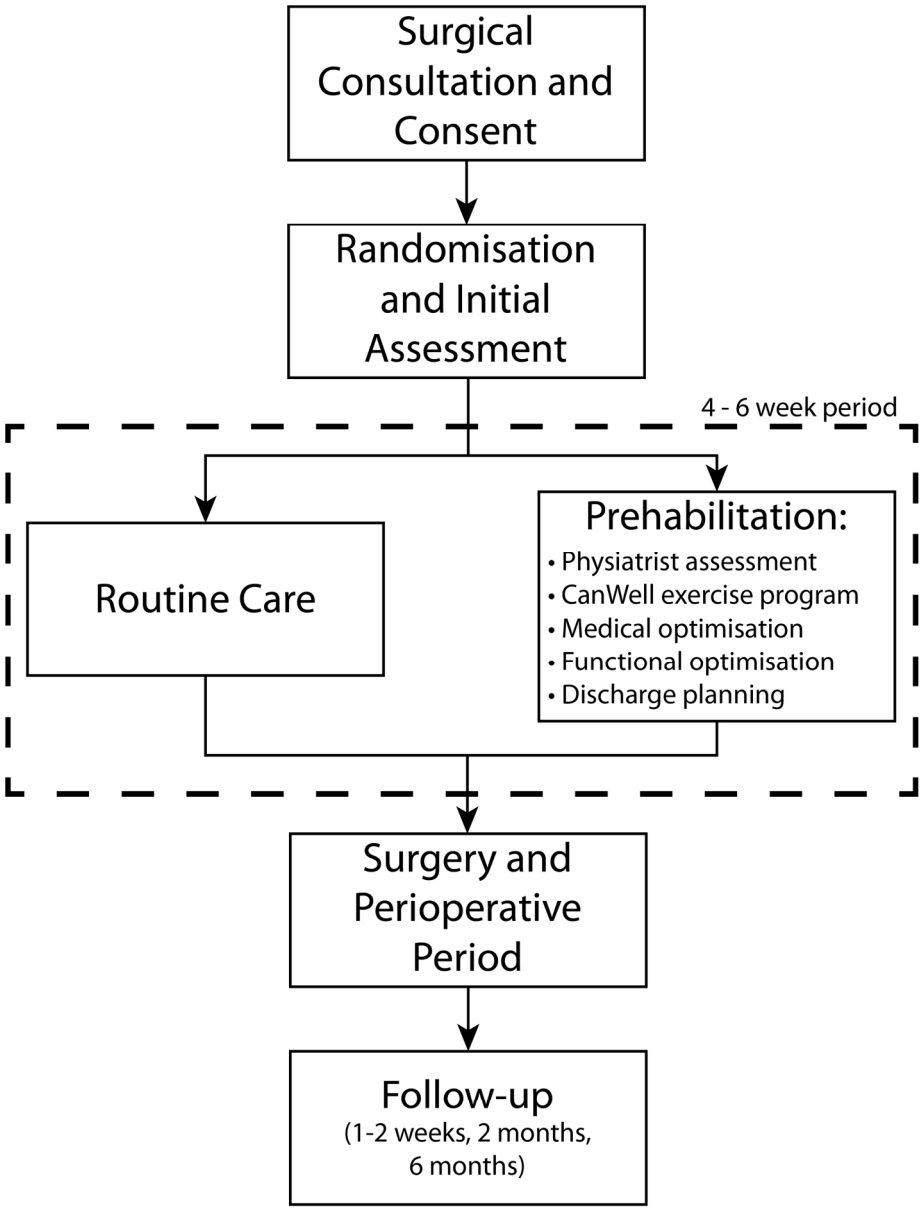

Figure 1: Study Participant Flow Chart

155x204mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 10
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 5 - 10, 12
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10 - 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 - 5
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4 - 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5 - 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7 - 8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10 - 11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8 - 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7 - 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8 - 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 - 9, fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5 - 6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6 - 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6 - 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6 - 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8 - 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7 - 9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10 - 11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10 - 11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10 - 11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10 - 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10 - 11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplement
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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ABSTRACT

Introduction: Prehabilitation interventions have shown efficacy in the orthopaedic and cardiothoracic surgical populations, but there has been limited evidence for general surgical patients. We present the protocol for a pilot trial of a novel prehabilitation intervention, consisting of a physiatrist-directed preoperative assessment and treatment program.

Methods and Analysis: This is a single-centre pilot randomised controlled trial investigating physiatrist-directed prehabilitation for a 4- to 6-week preoperative period. We will block-randomise 40-50 participants awaiting surgery for colorectal cancer to prehabilitation *versus* control. Participants in the prehabilitation arm will undergo assessment by a physiatrist and enrol in a supervised exercise program. The control group will not undergo any prehabilitation interventions in the preoperative period. Our primary outcome is feasibility, measured by examining recruitment, refusal, retention, and adherence rates as well as participant satisfaction and feedback. Secondary outcomes include physical fitness, functional ability, health-related quality of life, postoperative complications, mortality, readmissions, length of stay, prehabilitation interventions performed, and exercise complications.

Ethics and Dissemination: This study has been approved by the Hamilton Integrated Research Ethics Board (HIREB reference number 2015-0090-GRA). The results of this pilot study will be used to design a full-scale study and published in peer-reviewed journals.

Trial Registration Number: NCT02531620 (clinicaltrials.gov)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to investigate the feasibility of a physiatrist-directed prehabilitation intervention on the postoperative recovery of colorectal surgery patients
- A physiatrist-directed prehabilitation intervention is novel to the colorectal surgery literature
- The small size of this pilot is intended to estimate effect sizes and determine feasibility for a full-scale trial
- Few studies address patient functional recovery in domains other than fitness; this study intends to contribute to that body of evidence
- This trial is limited to a colorectal surgical patient population at a single academic centre

INTRODUCTION

Surgical interventions are significant stressors, particularly to the comorbid patient, which can significantly decrease their functional ability. In order to return to independent or assisted living at home, a minimum functional level is required[1]. Minimal function includes all physical and cognitive aspects of function. Prehabilitation refers to enhancing functional capacity of an individual to enable them to withstand an incoming stressor[2], and may encompass one or more domains of overall function.

Prehabilitation for elective surgical patients may be an effective intervention to improve baseline functional reserve, which is theorized to allow the postoperative patient to more quickly reach their minimal functional level. Study of prehabilitation interventions in cardiac and thoracic surgery patients have shown decreases in pulmonary complications, measures of physical function, and length of stay[3–5]. A meta-analysis of total hip replacement patients has also shown improvement in postoperative pain and self-reported function with exercise prehabilitation[6].

There has been increasing interest in prehabilitation in the abdominal surgical population. Selected primary studies in the abdominal surgery population are listed in table 1. The preponderance of current literature in this population describe cardiorespiratory fitness interventions, including exercise, inspiratory muscle training (IMT), and combinations of the two. Several studies from McGill University have investigated multimodal prehabilitation,

addressing dietary, exercise and psychologic domains[7,8]. Only one study found included focused functional training with the prehabilitation intervention[9].

Table 1: Primary Studies in Prehabilitation for Abdominal Surgery

Author	Country	Population	Intervention
Exercise Only			
Burke *et al.* [10]	United Kingdom	Colorectal	6 weeks, 30 min. daily supervised exercise.
Cho *et al.*[11]	Japan	Gastric	4 weeks, Aerobic 3-7x/week, resistance 1-2x/week, stretching.
Debette-Gratien *et al.*[12]	France	Transplant Hepatobiliary	12 weeks, 2x/week: 20 min. aerobic, 20 min. strength per session.
Dunne *et al.*[13]	United Kingdom	Hepatobiliary	12 sessions over 4 weeks. 30 min. aerobic exercise per session.
Kim *et al.*[14]	Canada	Colorectal	4 weeks. Home-based aerobic exercise prescription.
Timmerman *et al.*[15]	The Netherlands	Abdominal	Variable duration of intervention, 2x/week. 2 hours aerobic and strength exercise per session.
West *et al.*[16]	United Kingdom	Colorectal	6 weeks. 40 min. aerobic exercise daily.
Inspiratory Muscle Training (IMT) Only			
Barbalho-Moulim *et al.*[17]	Brazil	Bariatric	2-4 weeks. 6x/week, 15 minute IMT session.
Dronkers *et al.* (2008)[18]	The Netherlands	AAA*	2+ weeks. 6x/week. Daily deep breathing exercises and IMT.
Kulkarni *et al.*[19]	United Kingdom	Abdominal	*One of the following for 2-3 weeks:* Group A: Control; Group B: Deep breathing exercises; Group C: incentive spirometer; Group D: inspiratory muscle trainer
IMT and Exercise			
Carli *et al.*[20]	Canada	Colorectal	*One of the following for 3-6 weeks:* Bike/Strength Group: daily cycling 30 min., strength 10-15 min. Walk/Breathing Group: daily walking and breathing prescription.
Soares *et al.*[21]	Brazil	Open abdominal	2-3 weeks, 2x/week. 50 minute supervised sessions (stretching, IMT, upper/lower extremity exercises, walking, relaxation).
Diet and Exercise			
Baillot *et al.*[22]	Canada	Bariatric	12 weeks: Standard of care (dietician, physical activity consultation) AND 30 min. aerobic and 20-30 min. strength training, 2x/week.
Kaibori et al.[23]	Japan	Hepatobiliary	1 month: Exercise (60 min. walking and stretching, 3x/week) AND diet (Protein and sodium restriction).
Multimodal			
Dronkers et al. (2010)[9]	The Netherlands	Colorectal	2-4 weeks: 60-minute supervised session, 2x/week (resistance, IMT, aerobic, functional training) AND 45 minute daily home exercise (walking, cycling, IMT)
Gillis et al.[7]	Canada	Colorectal	4 weeks: Exercise (kinesiologist consult, 50 min. aerobic/resistance 3x/week), diet (dietician, nutrition prescription) AND psychology (psychologist to teach coping strategies).

Li et al.[8]	Canada	Colorectal	Variable duration: Exercise (kinesiologist, 30 min. aerobic/resistance 3x/week), diet (dietician, whey protein supplement) AND psychology (psychologist for anxiety reduction).

**Abdominal Aortic Aneurysm*

Despite the heterogeneity of the interventions studied, prehabilitation has been shown to improve physical fitness[8,12,13,21–23], respiratory function[9,17,21,23], and quality of life[13,22]. Single studies have also found small, statistically significant improvements in postoperative functional measures and complications. A study by Soares *et al.* showed an improvement in Functional Independence Measure (FIM) score in the prehabilitation group at 7 days following surgery, but no difference at either the preoperative period or at 30 days[21]. One study in the abdominal surgery literature reported a statistically significant difference in postoperative complications: in a gastrectomy population, Cho *et al.* reported a decrease in all-cause complications (Clavien-Dindo Grade I-V) in the exercise group[11].

Prehabilitation for abdominal surgery is promising, but continues to be in need of additional primary data. A recent meta-analysis showed that prehabilitation interventions could reduce the incidence of postoperative all-cause and pulmonary complications, and improve physical fitness[24]. This finding is qualified by the poor quality of evidence noted by the authors. Another meta-analysis additionally noted a small, statistically-significant decrease in length of stay, but this appears to have been mainly driven by the results of studies in the cardiovascular and orthopaedic populations[25].

Our pilot study uses a comprehensive physiatrist assessment as the main intervention, which is a novel approach in abdominal surgery. We note that the population of patients undergoing elective cancer resections are significantly different from the orthopaedic and cardiovascular patient populations. For this reason, it is hypothesized that a physiatrist-directed assessment addressing multiple functional domains may do more to improve patient functional status than a fitness intervention alone. There continues to be a need for primary data in this area, and this study hopes to provide more insight into the question.

METHODS AND ANALYSIS

This is a single-centre pilot randomised controlled trial to examine the effect of a physiatrist-directed prehabilitation intervention *versus* routine care. The primary objective of this study is to determine the feasibility of conducting an adequately powered study with a similar design and intervention. Feasibility will be assessed through recruitment rate, refusal rate, retention rate, adherence rate, participant satisfaction, and participant feedback. The secondary objective is to assess the effect of the intervention on measures of patient outcomes, including fitness, quality of life, function, perioperative complications, mortality, length of stay, and readmissions. The study design is shown in figure 1.

A randomized study design was selected to identify potential logistical issues prior to scaling to a full-scale study. The current study intervention requires patient visits to a surgeon, physiatrist, and the supervised exercise program, all of which must occur within a short 4- to 6-week period. Randomization adds additional scheduling challenges, as the timing of recruiting

participants into the intervention group is more unpredictable. Understanding these logistical challenges would be valuable to planning a full-scale study, and would allow further optimization of the intervention and study methodology.

The study will be conducted at St. Joseph's Healthcare Hamilton, a large Canadian urban academic hospital. Appropriate research ethics board approval has been obtained for this study.

Participants

We anticipate recruiting 40-50 study participants (20-25 per group) to the study over the course of 20 months. As many of the outcome measures utilized in this study have not been used in prehabilitation studies involving colorectal cancer patients, limited information on effect size and minimal clinically important difference was available for formal sample size calculations. The average sample size of the comparable studies listed in table 1 is 41. Accordingly, this pilot study aims to recruit 40-50 patients. This pilot study will enable us to collect the preliminary data we require in order to perform an accurate sample size calculation for the full study.

The recruitment period was estimated using recruitment rates of comparable studies. The majority of studies reported a recruitment rate between 2.5[15] and 4.7[20]. Assuming a recruitment rate of 3 participants per month and a 15% dropout rate, we estimate that the intended recruitment will be reached within a 20-month period.

Inclusion criteria:

Adults with age > 18; diagnosis of primary colorectal cancer appropriate for resection; English-speaking or with accessible interpreter; and frail, based on a score of 1 or greater on the Cardiovascular Health Study (CHS) frailty scale[26] or a history of falls in the past month, stroke or chronic pain.

Exclusion criteria:

Exclusion criteria for this study will include: need for emergent resection or procedure; extensive metastatic or unresectable disease; unwillingness to participate in the CanWell program; or unwillingness to be assessed by the study physiatrist. All study participants will be enrolled in the CanWell exercise program, which independently screens and excludes patients with: inability to ambulate, acute medical conditions, fever, chest pain or injuries[27]. Participants ineligible for the CanWell program will be excluded from CanWell only, and will continue with the remainder of the study and physiatrist-directed interventions.

Participants with pre-existing stroke, cardiac disease, impaired respiratory function or other premorbid conditions are intentionally *not* excluded from this study. We theorize that this population has functional deficits in IADLs and ADLs that may benefit from focused

interventions recommended by the study physiatrist, even in the absence of an exercise program.

Recruitment and Randomisation

Consenting patients referred to a study surgeon for colorectal cancer assessment will be evaluated by the research coordinator for eligibility. Written informed consent will be obtained from all study participants by the study coordinator prior to randomisation.

Study participants will be randomised with an equal (1:1) chance of being allocated to one of the two arms. A computer-generated randomisation log will be created by the study biostatistician. This log will be input into REDCap[28], a secure computer-based research system, and used sequentially to perform randomisation. Blocked randomisation will be used to ensure an equal number of participants in each arm. Randomisation allocation will occur by the study coordinator accessing the REDCap randomisation log at the time of enrolment.

Study Arms

Participants in the study will be randomised to either an intervention or control arm. The intervention arm will undergo a complete preoperative assessment by a physiatrist, followed by directed prehabilitation interventions to address functional or cognitive barriers to successful postoperative rehabilitation. In addition, all participants in the intervention group will be enrolled in the CanWell supervised exercise program. The control group will undergo routine

preoperative care. Following a 4- to 6-week preoperative period, both groups will proceed to their scheduled operative procedure. This 4- to 6-week period represents the average duration from initial surgical assessment to operative resection seen in our patient population. Both study arms will assess outcomes at baseline, perioperatively, and postoperatively at 1-2 weeks, 2 months, and 6 months.

Control Group

The control group will undergo no specific intervention in the preoperative period. This reflects the current standard of care.

Intervention Group

The intervention arm will be seen within 1 week after initial referral for a comprehensive assessment by a physiatrist. Following initial assessment, the participant will be given recommendations for preoperative optimisation. All participants in the intervention arm will also be enrolled in the CanWell supervised exercise program[27]. There will be a 4- to 6-week period from initial consultation to operative resection in which the recommendations will be put into place.

CanWell Supervised Exercise Program

The CanWell program consists of a 12-week exercise program, with two supervised exercise sessions and one unsupervised home exercise session per week. Study participants will be enrolled and will participate with the general CanWell participant population. Study participants will undergo the published exercise protocol[27], except that the program will be interrupted after the 4- to 6-week preoperative period for surgery. Following surgery, the participant will be assessed for safety at the 1- to 2-week follow-up appointment by their surgeon. If there are no contraindications to exercise at this assessment, the participant will complete the remainder of the 12-week program.

Enrolled participants are screened prior to participation; those with an inability to ambulate, active medical contraindications, fever, chest pain or injuries are excluded. The exercise prescription is then individualized by a kinesiologist based on baseline testing and contraindications, and includes aerobic exercise, muscular strength training, and flexibility exercises. Study participants who are excluded from the CanWell program at safety screening may continue with their physiatrist assessment and will be assessed with the intervention group on an intention-to-treat basis.

Physiatrist Assessment and Intervention

Maintenance of participants' functional well-being is a fundamental goal of the physiatrist-directed intervention. Studies have indicated that a thorough assessment of the impact of illness on physical, mental, and psychosocial functioning is an essential element of clinical diagnosis, a major determinant of therapeutic choices, a measure of their efficacy, as well as a

guide in the planning of rehabilitation services in cancer patients[29]. Measures of functional competence embracing the domains of activities of daily living (ADLs), instrumental activities of daily living (IADLs), environmental conditions, mental status, and emotional and psychosocial functioning have been increasingly used for this purpose.

The physiatrist's role for this intervention is a comprehensive assessment of the patient to identify impairments (e.g. pain, neuropathy, weakness, stiff joints), deficits in IADLs (e.g. grocery shopping, driving, entering and exiting a car) and deficits in ADLs (e.g. eating, grooming, bathing, dressing, toilet transfers). Participants will be assessed for functional ability, symptoms, physical fitness and quality of life, using outcome measures discussed below. This will be combined with a thorough history and physical examination to identify any impairments in the musculoskeletal or neurological domains.

A prehabilitation plan will be prescribed based on this clinical assessment. This may include: starting treatment for unrecognized chronic disease; recommending appropriate referrals for comorbidities; arranging appropriate home modifications based on functional status; reducing polypharmacy as appropriate; arranging early education and motor skills assessments to prepare for stoma care; and recommending follow-up or further consultations in the postoperative period.

Outcome Assessments

The primary research question will assess feasibility of a full study by collecting estimates of refusal rate, recruitment rate, retention rate, adherence rates for each intervention, participant satisfaction through the Client Satisfaction Questionnaire 8 (CSQ-8)[30], and participant feedback through anonymous survey responses. Adherence to the CanWell program will be measured by attendance kept by CanWell staff, while adherence to the physiatrist intervention will be assessed by the study team during follow-up appointments.

The secondary research question will assess the effect of the intervention by collecting participant outcome measures of fitness, symptoms, function, and quality of life at initial enrolment, 1-2 weeks postoperatively, 2 months, and 6 months. At each follow-up, the research coordinator will assess fitness using the 6-minute walk test (6MWT)[31], and functional status using the UK Functional Independence Measure and Functional Assessment Measure (UK FIM+FAM) tool[32]. Symptoms and quality of life will be self-reported by the participant using the following validated measures: the Edmonton Symptom Assessment System (ESAS) [33], the Short Form 36 health survey (SF-36)[34], pain on a Visual Analogue Scale (VAS)[35], and the Bowel Function Index (BFI)[36].

Perioperative outcomes will be collected by the study team and will include: complications classified using the Clavien-Dindo scale[37], 30-day mortality, length of stay, and readmissions within 6 months. Descriptive data will be collected regarding interventions performed and adverse events during the prehabilitation intervention. Any exercise-related adverse events will

be described using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[38].

Statistical Analysis

To assess our primary research question, we will follow intention-to-treat principles, including all participants who enrolled in the study in our feasibility analysis. The recruitment rate, refusal rate, retention rate, and adherence rate will be reported as relative frequencies with 95% confidence intervals. Participant satisfaction scores on the CSQ-8 will be compared through an independent t-test. Lastly, two independent researchers will review all participant survey responses for common themes. Any discrepancies will be resolved through consultation with a third member of our research team.

To assess our secondary research question, descriptive statistics that describe our sample (means and standard deviations) will be calculated and sorted by group. A split-plot ANOVA will then be performed for each outcome measure. The condition (intervention or control) will be the between-group factor with two levels. Time (1 -2 weeks, 2 months, 6 months) will be the within-group factor with three levels. A Bonferroni correction will be applied to correct for multiple comparisons. Statistical significance will be considered at $p \leq 0.05$. All analyses will be completed in SPSS Version 24.

Blinding

Due to the nature of the prehabilitation intervention, it is not possible to blind the study staff, outcome assessors and participants. Statistical analysis of secondary outcomes will be blinded to study arm.

ETHICS AND DISSEMINATION

The main objective of this study will be to collect pilot data to support the design of a full-scale clinical trial. Study results will also be presented in relevant scientific meetings and published in peer-reviewed journals.

This trial has been approved by the Hamilton Integrated Research Ethics Board (HIREB; reference number 2015-0090-GRA), which has the independent authority to audit trial conduct. Any amendments to the trial protocol will be submitted to HIREB for approval. The trial is registered with clinicaltrials.gov with the study identifier NCT02531620 since August 15, 2015.

Adverse Events

The main adverse events anticipated in this study are risks of injury or harm occurring during the exercise intervention. To minimize the risk of harm, participants are evaluated by their surgical team, the study physiatrist, and the study coordinator for contraindications to exercise during the initial assessment. The participant will also be screened for safety by CanWell staff prior to exercise, and subsequently monitored for harm during the exercise intervention. Any patient with contraindications to exercise will be excluded from the CanWell program, but will

otherwise continue with the other prehabilitation interventions as directed by the study physiatrist.

Data Management and Monitoring

Study data will be stored on a secure, encrypted server. Any data that must be retained in paper format will be stored in a secure location, accessible only to the study team. A study management team consisting of the principal study surgeon, research assistant, study physiatrist and research resident will meet at least monthly to ensure study implementation. Due to the small sample size, no independent data monitoring committee will be established.

Participant Considerations

Participants will not be remunerated for their participation in this study. All fees associated with the study will be reimbursed, including parking fees for study appointments and membership fees for the supervised exercise program.

Participants may withdraw their consent for participating in this study at any time, and will be given an opportunity to give reasons for withdrawing from the study. Participants who withdraw from the study will continue to receive routine surgical care.

DISCUSSION

The primary goal of this study is to collect feasibility data in support of a full-scale study in the future. Pilot data will be used to refine our methodology and calculate an appropriate sample size. A randomized design was selected to assess the potential logistical challenges of such a program in a small sample. In the current abdominal surgical literature, prehabilitation interventions have addressed cardiorespiratory fitness, nutrition and psychological coaching. Only one previous study of prehabilitation for abdominal surgery included functional training in their program[9]. We theorize that functional recovery following surgery can be improved with focused prehabilitation interventions to address specific functional deficits. We believe that a physiatrist has the clinical knowledge and expertise to identify and address such deficits. To our knowledge, this is the first trial to study the feasibility of a physiatrist-directed prehabilitation intervention for colorectal cancer patients.

AUTHORS' CONTRIBUTIONS

NA conceived the idea of the study. SGW led protocol development, wrote early drafts of the study protocol, prepared the Institutional Research Board submission, and is responsible for the day-to-day conduct of the study. EM and DH provided rehabilitation and physical medicine expertise, and performed clinical functional status assessments. NW and RS provided analytical advice and support. All authors commented on this protocol.

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COMPETING INTERESTS

Drs. Wong, Maida, Harvey, Sonnadara, Amin and Ms. Wagner have no conflicts of interest or financial ties to disclose.

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TABLES

Table 1: Primary Studies in Prehabilitation for Abdominal Surgery

FIGURES

Figure 1: Study Participant Flow Chart

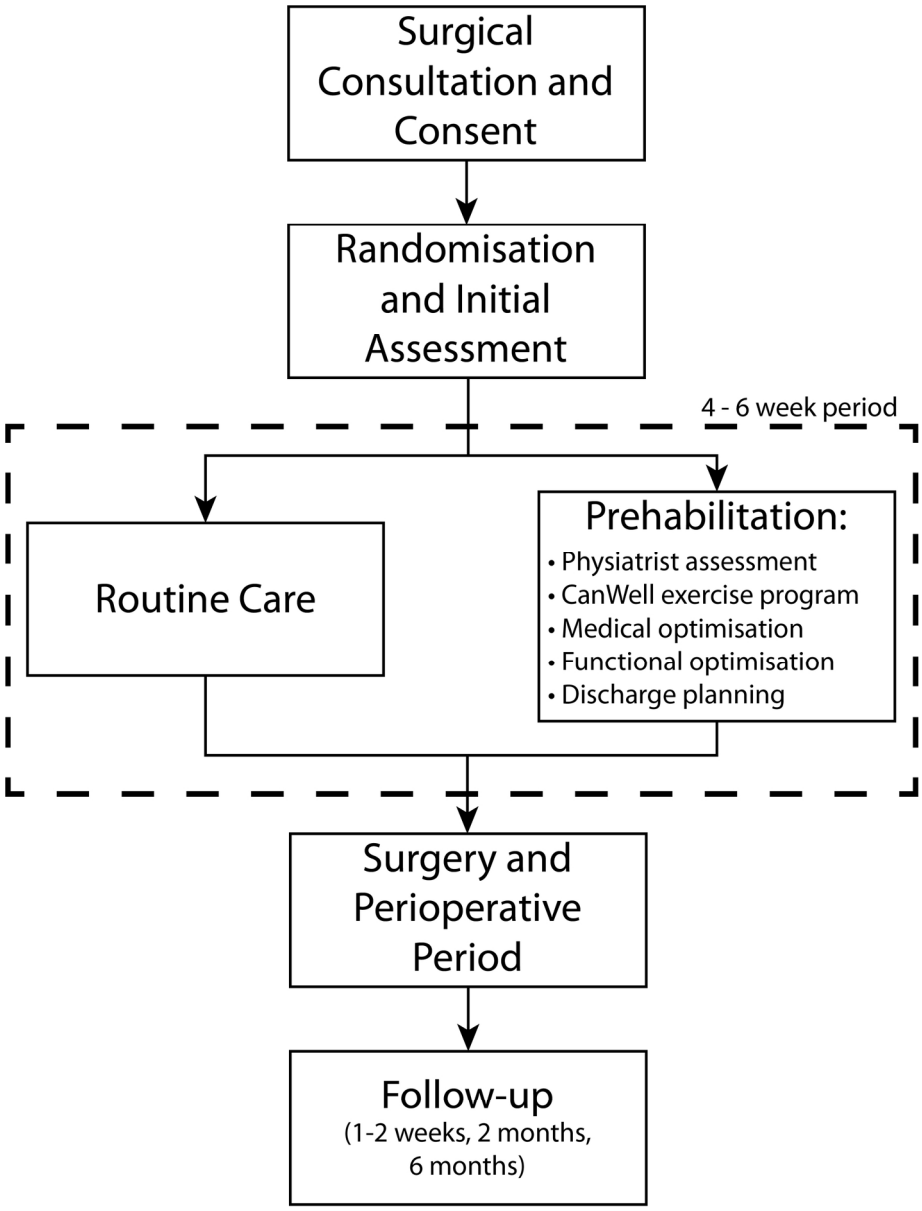

Figure 1: Study Participant Flow Chart

155x204mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 10
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 5 - 10, 12
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10 - 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 - 5
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4 - 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5 - 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7 - 8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10 - 11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8 - 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7 - 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8 - 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 - 9, fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5 - 6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6 - 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6 - 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6 - 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8 - 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7 - 9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10 - 11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10 - 11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10 - 11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10 - 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10 - 11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplement
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.